# PULMONARY CIRCULATION

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# PULMONARY CIRCULATION

## An International Symposium. 1958

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*Edited by* WRIGHT R. ADAMS, M.D.
*and* ILZA VEITH, PH.D.




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# Preface

RECOGNITION OF THE EXISTENCE of pulmonary circulation preceded Harvey's discovery of the total circulation of the blood by almost a century. But although 400 years have passed since it was first described, our knowledge of the pulmonary circulation is still far from complete The growing realization of its significance in many diseases of the heart and the lungs has provided the impetus for numerous studies of its physiology, anatomy, pathology and pathologic physiology. But even today, damage to the pulmonary arteries is often the limiting factor in the correction of congenital and acquired heart disease The surgeon may repair a heart lesion associated with pulmonary hypertension only to see his patient die because of irreversible damage to the pulmonary vascular bed Resection of a lung, or a part thereof, is often limited by the state of the pulmonary vasculature In many nonsurgical conditions pulmonary hypertension with resulting obstruction of the vascular bed, or disease of the vessels from other causes, is the principal cause of death.

Many aspects of the pulmonary circulation still await clarification. We know that the pulmonary arteries in the fetus have relatively heavy muscular walls and that sometime after birth the vessels change when the media thin out and the vessels gradually take on the adult form. But this change does not occur if high arterial pressure in the pulmonary circuit persists after birth, and eventually some of the branches become obstructed by intimal proliferation Little is known about the time sequence of these changes, the rate at which they develop is variable, but the causes for the variation have not yet become clarified Is the vascular disease associated with hypertension resulting from mitral stenosis similar to that seen in congenital heart disease? Is the pulmonary hypertension seen in pulmonary emphysema similar to that in heart disease? To what extent will pathologic changes in the arteries regress if the cause of hypertension is removed? To what extent will drugs modify the pulmonary circulation? These and many other questions have been raised by physicians

Physiologists and pathologists are devoting increased effort to their search for the answers to the practical questions and to gain a general understanding of the lesser circulation In this they have been aided by many new methods physiological, pathological and radiological techniques have been developed rapidly and have been used on normal subjects, on patients and on animals And yet, some of the results have been confusing, for different methods seem to yield different answers

Because of the urgency of the situation the Chicago Heart Association decided to sponsor an international conference on the subject It was felt by the committee in charge of the event that knowledge of the subject would be greatly enriched if it were made possible for a group of active investigators to express their concepts, to present results of their recent researches and to discuss their experiences with each other. A conference was held at the

Palmer House in Chicago on March 20, 21 and 22, 1958, and this volume is its result There is little doubt that these proceedings will be of interest to all students of the pulmonary circulation and also to physicians who face practical problems of diagnosis and treatment in the field.

The conference was an unusual one inasmuch as it was "closed" in the sense that participation in the discussion was restricted to the invited symposium members and a very small number of guests, but "open" in the sense that there was a large audience—a very enthusiastic and attentive one. The conference was divided into five half-day sessions. The morning of Thursday, March 20, was devoted to the physiology of the pulmonary circulation, the afternoon to the pathology of the pulmonary circulation. On the morning of Friday, March 21, the topic was the pulmonary circulation in primary lung disease, and in the afternoon the pulmonary circulation in congenital heart disease was discussed The closing session, on Saturday morning, March 22, was devoted to the pulmonary circulation in acquired heart disease

No attempt was made to cover all phases of the subject or all diseases which involve the pulmonary circulation Emphasis was always placed on new knowledge and its significance and interpretation Obviously the subject matter did not lend itself to a division as clear-cut as is indicated by the titles of the sessions However, the emphasis on the various categories was always maintained and the different sessions approached the same subject from distinctive points of view

Two committees of the Chicago Heart Association joined in formulating the idea of the conference They were the Professional Education Committee and the Postgraduate Education Committee Dr Louis N. Katz, who was the president of the Heart Association during the earliest planning stages of the conference, gave his vigorous support to the idea and appointed a special committee for its development This committee, composed of Chicagoans, selected Dr. Julius Comroe, Jr, Dr Jesse Edwards, Dr. Lars Werko, Dr. Howard Burchell and Dr Paul Wood as the chairmen of the five sessions Five members of the Chicago Planning Committee were chosen to serve as co-chairmen In addition to arranging their own sessions the chairmen collaborated with the local committee in the general planning and organization of the symposium *The Chicago Heart Association owes these men a large debt* of gratitude for their enormous contribution to a truly successful meeting

Dr André Cournand also deserves special thanks Following a dinner held on the evening of Thursday, March 20, he presented a brilliant historical review of the subject which appears as the first chapter of this volume.

Many of the papers and discussions were profusely illustrated with slides The essayists were most helpful in reducing the number of illustrations so that a volume of reasonable size could be achieved. The editors, however, must bear the onus for further deletions It is hoped that these deletions have not seriously impaired the clarity of the presentations For reasons of space the editors also found it necessary to abbreviate some of the discussion. This may have diminished some of the spontaneity and inadvertent humor of the meeting but it doubtless added to its conciseness

The Heart Association and the symposium committee acknowledge the faithful attendance and active participation in all sessions by all of the participants. The staff of the Heart Association contributed above and beyond the call of duty. Appreciation is also due our Publisher, Dr Henry M Stratton, who attended the symposium and gave us much valuable advice for its publication

If the understanding of pulmonary circulation has been advanced by this symposium and if it provides the impetus for further study on the subject, the efforts of all those connected with it are amply rewarded.

WRIGHT R. ADAMS
ILZA VEITH

*Chicago, 1958*

# I. THE HISTORICAL DEVELOPMENT OF THE CONCEPTS OF PULMONARY CIRCULATION

*By* André Cournand

According to reliable authorities, it is a sign of age when an investigator chooses to look backward rather than forward. In order to dispel any such thought from the minds of my friends here, I should like to examine at the outset my reasons for selecting a historical subject for this after-dinner speech. Did I wish to demonstrate my curiosity, or was I moved by the vain desire to appear before you as a scholar? Did I seek satisfaction of a purely aesthetic pleasure related to the re-examination of old modes of thought? Unless I delude myself, a more profound urge guided my choice, a youthful urge, if I may say so, in which can be discerned the following expressions of cultural and human and personal interests: To apprehend the progressive conquest of knowledge in its actual state and thereby give a logical form to intellectual genealogies, to establish a census of epistemological obstacles which have been surmounted; to identify myself with other human beings who have spent a vast deal of energy on matters in which excellence is difficult to achieve and which procure moments of serene satisfaction rarely indeed; to search for flaws in the reasoning and in the techniques of men who are considered admirable; to understand the period in which they lived, and the circumstances leading to their scientific achievements and to their progress in knowledge or in technique, more urgently, to become aware of the impact of philosophy, dogmatism and authority upon the fruits of free inquiry.

In this mood, I shall now present some remarks on the historical development of the concept of pulmonary circulation, limiting my subject to the following three topics

1 The progressive elaboration of the concept of forward movement of the blood through the lungs from the right to the left ventricle.

2 The gradual unveiling of the object served by the blood in transit through the lungs

3 The earliest and significant acquisitions concerning the dynamics of the pulmonary circulation

## Progressive Elaboration of the Concept of Forward Movement of Blood through the Lungs

The progressive elaboration of the concept of unidirectional movement of blood from the right to the left ventricle extends from the second to the middle of the seventeenth century Four contrasting and strong personalities exemplifying man in search of truth contributed mostly to the exact descrip-

tion of the forward motion of blood in transit through the lungs: Claudius Galen, Michael Servetus, William Harvey, and Marcello Malpighi

*Claudius Galen* Born in *130 A.D.* in Pergamum, Asia Minor, Galen came to Rome in *161* by way of Smyrna, Corinth and Alexandria In the Capital of the Roman Empire, then at the zenith of its power and splendor, he became the private physician of, and was befriended by the Emperor Marcus Aurelius, like him, a stoic philosopher, and an ardent Hellenist.[1] John F. Fulton, in the first chapter of his scholarly and eloquently moving monograph on "Michael Servetus, Humanist and Martyr,"[2] has concisely analyzed the contribution of Galen to the physiology of the nervous system and of the circulation. There he gives great credit to some of Galen's inspiring experimental neuro-physiologic studies in man and in pigs; and he wonders why, when it came to the vascular system, "his keen intuitive sense forsook him" I should like to present a less severe point of view and to emphasize the valuable part played by Galen in the discovery of the true passage of bloods through the lungs.

He commenced the discovery by refuting the doctrine of Eristratus According to the latter, a member of the famous Alexandrian School, the circulation as we know it now, was divided into two distinct systems separated in the heart by a septum which presented pores: (1) a venous or sanguinous system through which blood, moving by ebb and flow, was eventually carried to all viscera and to the extremities and (2) an arterial or aerial system of channels through which air drawn by the trachea artery into the lungs reached the left ventricle through the venous artery (pulmonary vein) and was finally distributed to the body

Galen's refutation is fundamentally based on the experimental demonstration that arteries contain blood His permanent contribution to our knowledge of the pulmonary circulation may be stated briefly and in modern language as follows· (1) The blood moves forward from the pulmonary artery into the lungs and thence into the pulmonary veins and the left ventricle, (2) this unidirectional transit of blood is favored by respiratory movements and by the presence of valves at the origin of the pulmonary artery; (3) two distinct bloods exist, the spiritual and the venous one which has, the other which has not been purified by respiration, the first formed in the left ventricle and distributed through the arteries, the second formed in the liver and found in the veins and the right ventricle This separation of the two kinds of blood within the two ventricular cavities of the heart led him to the much heralded postulation of small invisible pores through the interventricular septum Through these holes some blood was exuding and a certain proportion of spirit reached the right ventricle, the venous system and the pulmonary artery, and added a vital property to the natural or nutritive property of the venous blood Compounding this erroneous view, Galen thought also that the blood in the pulmonary artery was nourishing the lungs

We may well wonder why a man justly acclaimed as the founder of practical modern anatomy and experimental physiology should have assumed the existence of pores, even of pores too small to be visible. In his scholarly article on "Galen's view of the vascular system, in relation to that of Harvey," Prendergast[2] demonstrates with the aid of texts that the postula-

tion of septal foramina was the outcome of a purely mechanical view concerning the activity of the heart and of some anatomical considerations related to the size of its four orifices. The argument, somewhat specious, runs as follows: the size of the pulmonary artery orifice through which blood leaves the right ventricle is smaller than that of the tricuspid orifice; therefore, when the heart contracts, some blood must be forced out through the small pits or depressions of the septum; the supposed inverse disparity between the size of the aortic and mitral orifices would seem to lend corroboration to this conclusion These pits were therefore not fortuitous arrangements but had developed according to a design and in order to serve a purpose. Here, we observe the evils of a certain form of teleological reasoning in an intellectual giant, whose philosophic, scientific, historical and medical output adding to 500 treatises, of which 128 have survived fire and destruction, is the culmination of all antique knowledge

Nevertheless, the invisible pores, together with all the theories propounded by Galen, became the official medical doctrine of the Church which, built on the ruins of the Roman Empire, had necessarily recourse to dogmatism and authority in its access to and maintenance of power Ironically, while some of the errors in reasoning of Galen endured, the objective creations of this stoic philosopher, the descriptive anatomy and experimental physiology, remained dormant for nearly 1,500 years.

*Michael Servetus.* Let us now jump over this interlude and meet Michael Servetus[2,4] (fig 1), a scholar of the early Renaissance in revolt against dogma and the blind acceptance of the official interpretation of biblical texts A theologian who could not find any support for the Doctrine of the Trinity in the Greek and Hebraic bibles A philosopher, influenced by the resurgence of the platonic school in Florence, who believed that all forms of human knowledge theology, philosophy, psychology, anatomy, physiology, mathematics, geography, astronomy and astrology with each of which he was personally familiar, were ultimately to be unified in one single coherent system of the Universe, not only penetrated by Reason as the Stoics held, but by a creative dynamic energy, the very being of the Creator who infuses all with his spirit A Christian, with reverence and love for the supreme harmonious being, who fought for the return to a simple faith, that of the early Christian Era A man of indomitable courage and absolute intellectual integrity, forthright in the expression of his views, unyielding in matters which he considered to be the truth, who thereby had few devoted friends and made many enemies A martyr who in his final agony on the stake spoke his innermost, uncompromising belief that Jesus was the son of the eternal God, and not eternal himself

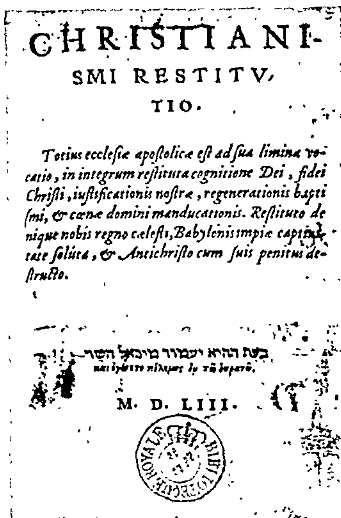
The life of this prominent figure of the sixteenth century, spent in great part in France, is almost a continuous flight From the province of Navarre, in Spain, where he was born, in *1511*, we follow him to Villanueva, where he was reared, to Toulouse where he studied law, to Bologna in Italy where he dejectedly attended the coronation of Charles V of Spain by Pope Boniface VI, to Basel where he studied Aryanism, to Strasbourg where in *1531*, at the age of 20, he published his treatise on the errors of the Trinity, to Basel




FIG 1.—Portrait of Michael Servetus. Frontispiece of the book, *Hunted Heretic*, by R M Bainton [4]

again where he assumed the name of Villanovanus, in order to hide from and to escape the Inquisition, to Paris where he taught mathematics, to Lyons where he met his friend the physician, Symphorien Champier, edited anew the Geography of the Ptolemees, and created comparative geography, and again in Paris by *1537*, where he started to study medicine under Dubois, Fernel and Guenther, to learn anatomy by dissection as the colleague of Vesalius, where he wrote on syrups and medical astrology and fought with the Dean of the Medical Faculty. This lonely man, never secure, finally settled as a physician near Lyons, in the town of Vienne There he practiced 12 years, apparently content, but, in secret, writing the book which made his name immortal but also was the cause of his arrest by the Inquisition on the denunciation of a friend of Calvin. Escaping from prison, he took flight to Geneva where, while attending church on a Sunday morning, he was recognized, expeditiously judged and burned at Champel, October the 27th, *1553*.

We now open one of the three remaining authentic copies of his book,



CHRISTIANI-
SMI RESTITV-
TIO.

*Totius ecclesiæ apostolicæ est ad sua limina vo-
catio, in integrum restituta cognitione Dei, fidei
Christi, iustificationis nostræ, regenerationis bapti
smi, & cœnæ domini manducationis. Restituto de
nique nobis regno cælesti, Babylonis impiæ captiui-
tate soluta, & Antichristo cum suis penitus de-
structo.*

בעת ההיא יעמוד מיכאל השר

καὶ ἐγένετο πόλεμος ἐν τῷ οὐρανῷ.

M. D. LIII.

Fig 2—Title page of the copy of the *Christianismi Restitutio* in the Bibliothèque Nationale, Paris

*Christianismi Restitutio,* printed with no indication of author, publisher or place in *1553.* This copy (fig 2) preserved at the Bibliothèque Nationale in Paris, was once in the hands of Colladon who helped his friend Calvin, throughout the trial of Servetus in Geneva It was saved from the pyre at Champel but suffered later from the effects of moisture. Browsing through Chapter 5, we reach page 170 and 171 (fig 3), and read there in a few sentences, luminous and concise, an almost complete and exact description of the pulmonary circulation The English translation from this Latin text, given underneath, follows very closely the French version of the physiologist, Marie Jean Pierre Flourens,[5] with here and there direct quotations from Roland Bainton's authoritative book on Michael Servetus, *Hunted Heretic*:[4]

"(The passage of the blood from the right to the left ventricle)—does not take place through the median partition of the ventricle as is generally sup-

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quã nunc audies. Hinc dicitur anima esse in sanguine, & [illegible]

[illegible]

diastolem attrahitur, apta suppellex, vt fiat spiritu [illegible]

Quòd ita per pulmones fiat cõicatio, & præparatio, [illegible] cet cõiunctio varia, & cõicatio, venæ arteriosæ cũ arteri venosa in pulmonibus. Confirmat hoc magnitudo insigne venæ arteriosæ, quæ nec talis, nec tãta facta esset, nec [illegible] a corde ipso vim purissimi sanguinis in pulmones emit [illegible] ob solũ eorũ nutrimentum, nec cor pulmonibus ha [illegible] ratione seruiret: cũ præsertim antea in embryone solerent pulmones ipsi aliunde nutriri, ob membranulas illas, [illegible] valu

LIBER V. 171

[illegible] cordis [illegible] non [illegible] aperta, [illegible] effunditur sanguis a [illegible] pulmone [illegible] copiose [illegible] pulmonibus ad cor non simplex aer, sed mixtus san- [illegible] per arteriam venosam ergo in pulmone [illegible] flauus ille color a pulmonibus datur san- [illegible] a corde. In sinistro cordis ventriculo [illegible] tantæ & tam copiosæ mixtionis, nec [illegible] illa sufficiẽs. Demum paries ille me- [illegible] & facultatum expers non est aptus [illegible] & elaborationẽ illam, licet aliquid re [illegible] artificio quo in hepate fit transfusio [illegible] ad venam cauam propter sanguinem, fit e- [illegible] in pulmone transfusio a vena arteriosa ad arte- [illegible] venosam propter spiritum. Si quis hæc conferat [illegible] quæ scribit Galenus lib. 6. & 7. de vsu partium, ve- [illegible] penitus intelliget, ab ipso Galeno non animad [illegible]

Ille itaq; spiritus vitalis a sinistro cordis ventriculo in [illegible] totius corporis deinde transfunditur ita vt qui te

[illegible]

[illegible] omnia cerebri penetrant, & ipsos cerebri ven- [illegible] interne succingunt, vasa illa secum compli- [illegible] & contexta seruantes, vsque ad neruorum origi- [illegible] eos sentiendi & mouendi facultas inducatur [illegible] illa miraculo magno tenuissimè contexta, [illegible] arteriæ dicantur, sunt tamen fines arteriarum, tenden

Fig 3—Pages 170 and 171 of the copy of the *Christianismi Restitutio*, containing the description of the pulmonary circulation.

posed, but by an elaborate device the refined blood is driven from the right ventricle of the heart over a long course through the lungs, where it is prepared and made flavus—bright or yellow—and thence passes from the arterial vein (pulmonary artery) into the venous artery (pulmonary vein)—et a vena arteriosa in arteria venosa transfunditur—"

"In order to understand how this communication takes place through the lungs, we must learn the connection, the multitude of unions of the arterial vein with the venous arteriosa in these lungs This view of the manner of communication is confirmed by the Caliber of the Arterial Vein (Pulmonary Artery) which would not be so large nor carry such an amount of blood to the lung if nutrition alone was to be provided for, especially since in the embryo the lung is nourished through other channels, and this blood does not reach it — It must then be for another purpose that the blood is sent in such abundance from the heart to the lungs immediately after birth; moreover, it is not simply air, but air mixed with blood which is sent from the lungs to the heart through the pulmonary vein, so that the mixture takes place in the lungs The yellow color is given to the spiritous (arterial) blood by the lungs and not by the heart In the left ventricle, there is no place large enough for so copious a mixture, nor is that elaboration sufficient for the bright tint Moreover, the middle wall, since it lacks orifice, is not suitable for this communication and elaboration"

The question has been raised in connection with this text whether Servetus enjoys a complete priority for the discovery of the pulmonary circulation With the help of a few quotations from Bainton's book, this question may be partly answered. "Here, as so often in the history of science, independent investigators came upon the same truth almost coincidentally. There can be no rivalry between Servetus and Columbo, the other contestant, for it has been established that neither knew the discovery of the other. In so far as the announcement, there is no problem at all" [4] Indeed, Servetus' text dates back to *1553* whereas Columbo's *De Re Anatomica* was published in *1559* Furthermore, with regard to the time of the observation, Bainton, in a short and searching paper,[6] has given convincing proof that a manuscript in the Bibliothèque Nationale (fig 4) containing the passage on the pulmonary transit of blood is most probably a faithful copy of an earlier draft which we know to have existed in 1546, a copy of which had been sent then to Calvin who never returned it. Ironically, I raise the question whether somehow Servetus' claim to fame was unwittingly consolidated by his tormentor

There is another claim to priority, impossible to ignore on the basis of chronology, but somewhat disputable on the basis of its significance In *1922*, an Egyptian medical student, Muhyi el-Din At-Tatawi, found in the Prussian state library, a text in Arabic, of the commentaries of the Canon of Avicenna by a Persian philosopher, philologue and physician, Ibn an-Nafis who lived in Alexandria during the thirteenth century In 1924 he published part of this text, in his thesis for the degree of Bachelor in Medicine,[7] which reveals that Ibn an-Nafis had rejected Galen's concept of the permeability of the interventricular septum two centuries before Michael Servetus, Vesalius and Columbo, and had also claimed that the aeration of blood took place in the lungs However, in his rather confused text, which can be read also in the German translation by Max Meyerhof,[8] the Persian scholar does not call attention to the size of the pulmonary artery and he asserts that some of the blood serves to nourish the lungs "was aber davon als wenig gelautert zuruck bleibt, *das verwendet die Lunge zu ihrer Ernahrung*" Nevertheless, it has been ascertained that Servetus had no knowledge of his Arabic predecessor [9]

A question more important than the priority of the discovery probably looms large in your mind Why these two pages of anatomic and physiologic description in a book devoted to the return to true Christianity? Bainton [4] has given an attractive answer to the question, but I doubt that this is the place to review his theological argument of which I shall cite only the conclusion "He who really understands what is involved in the breathing of man, has already sensed the breath of God, and thereby saved his soul" Obviously, respiratory physiologists can count themselves among the chosen ones!

For over a century, the description given by Servetus of the pulmonary circulation remained unacknowledged for fear of the Inquisition, and buried in the only three copies of his book which escaped destruction by fire Then in 1694, William Walton mentions, in his book *Reflections on Ancient and Modern Learning*,[10] that he had a transcription of the passage which I have read to you, from an English surgeon who had obtained it from an unnamed friend Three years later, in the second edition of the same book, Walton in-

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[illegible]

Ad quam rem est prius intelligenda substantialis gene-

[illegible]

...itam in se continens aquæ, aëris & ignis. Generatur ex facta in pulmonibus mixtione inspirati aëris cũ elaborato subtili sanguine, quē dexter ventriculus cordis sinistro communicat. Fit autem cõmunicatio hæc, non per parietem cordis mediū, ut vulgo creditur. Sed magno artificio a dextro cordis ventriculo, longo per pulmones ductu, agitatur sanguis subtilis: à pulmonibus præparatur, flavus

[illegible]

... diastolem attrahitur, apta suppellex, ut fiat spiritus vitalis.

Quod ita per pulmones fiat cõicatio, & præparatio, docet cõiunctio varia, & cõicatio, venæ arteriosæ cũ arteria venosa in pulmonibus. Cõfirmat hoc magnitudo insignis venæ arteriosæ, quæ nec talis, nec tãta facta esset, nec tãtam a corde ipso vim purissimi sanguinis in pulmones emitteret, ob solũ eorũ nutrimentum, nec cor pulmonibus hac ratione serviret: cũ præsertim antea in embryone solerent pulmones ipsi aliunde nutriri, ob membranulas illas, seu valvulas

LIBER V. 171

[illegible] ... in pulmonem ... ad cor ... non simplex aer, sed mixtus sanguine ... venosam ergo in pulmonibus ... flavus ille color a pulmonibus datur ... a corde. In sinistro cordis ventriculo ... ex tanta & tam copiosa mixtione, nec ... nulla sufficiés. Demum paries ille medius ... & facultatum expers non est aptus ... & elaborationē illam, licet aliquid re... ... quo in hepate fit transfusio ... ad venam cavam propter sanguinem, fit etiam in pulmone transfusio a vena arteriosa ad arteriam venosam propter spiritum. Si quis hæc conferat cum quæ scribit Galenus lib. 6 & 7 de usu partium, veritatem penitus intelliget, ab ipso Galeno non animadversam.

Ille itaq; spiritus vitalis a sinistro cordis ventriculo in arterias totius corporis deinde transfunditur, ita ut qui tenuior est, superiora petat, ubi magis adhuc elaboratur, præcipue in plexu retiformi, sub basi cerebri sito, in quo ex vitali fieri incipit animalis, ad propriam rationalis animæ sedem accedens. Iterum ille fortius mentis ignea virtute tenuatur, elaboratur, & perficitur, in tenuissimis vasis, seu capillaribus arterijs, quæ in plexibus choroidibus sitæ sunt, & ipsissimam mentem continent. Hi plexus intima omnia cerebri penetrant, & cerebri ventriculos interne succingunt, vasa illa secum complexa, & contexta servantes, usq; ad nervorum origines, ut in eos sentiendi & movendi facultas inducatur. Vasa illa miraculo magno tenuissimè contexta, tametsi arteriæ dicantur, sunt tamen fines arteriarum, tendentes

Fig 3—Pages 170 and 171 of the copy of the *Christianismi Restitutio*, containing the description of the pulmonary circulation

posed, but by an elaborate device the refined blood is driven from the right ventricle of the heart over a long course through the lungs, where it is prepared and made flavus—bright or yellow—and thence passes from the arterial vein (pulmonary artery) into the venous artery (pulmonary vein)—et a vena arteriosa in arteria venosa transfunditur—"

"In order to understand how this communication takes place through the lungs, we must learn the connection, the multitude of unions of the arterial vein with the venous arteriosa in these lungs This view of the manner of communication is confirmed by the Caliber of the Arterial Vein (Pulmonary Artery) which would not be so large nor carry such an amount of blood to the lung if nutrition alone was to be provided for, especially since in the embryo the lung is nourished through other channels, and this blood does not reach it — It must then be for another purpose that the blood is sent in such abundance from the heart to the lungs immediately after birth, moreover, it is not simply air, but air mixed with blood which is sent from the lungs to the heart through the pulmonary vein, so that the mixture takes place in the lungs The yellow color is given to the spiritous (arterial) blood by the lungs and not by the heart In the left ventricle, there is no place large enough for so copious a mixture, nor is that elaboration sufficient for the bright tint Moreover, the middle wall, since it lacks orifice, is not suitable for this communication and elaboration "

the fact that the vein-like artery and likewise the ventricle are always full of blood which must have come to them through the veins and by no other path than an intrapulmonary one." So much has been written about William Harvey during the past year and so well, that the task of discussing what is original, about his contribution to the description of the pulmonary circulation, is neither easy nor inspiring. I shall, however, try my hand and do it mostly in quoting relevant sentences translated from his celebrated book [11]

To begin with, Harvey used all the known resources of the static art of anatomy to demonstrate that the blood moves in one direction and could not move otherwise. He interpreted the role of the "elegant and contrived valves and fibers and other structural artistry of the heart," following or elaborating on the teachings or writings of the great anatomists of the Italian school, Vesalius and Fabricius

Then, he introduced an entirely new concept, that of the kinetics of blood motion. "The pulsation of the right ventricle (alternatively tension and contraction) forces the blood out of the chamber and propels it through the artery-like vein in the lungs" He also recognized the additional action of the breathing lungs, their "rise and fall, movement that necessitates the opening and closing respectively of the porosities and vessels" He furthermore emphasized that in all the animal world the presence of the right ventricle is always associated with that of lungs. "Nature where she ordained that the same blood should percolate the lungs saw herself obliged to create another ventricle, the right" He also disclaimed that the pulmonary blood was merely used for the nutrition of the lungs "It is altogether incongruous to suppose that the lungs need for their nourishment so large a supply of food, so pulsatorily delivered"

Finally, he did conceive of the pulmonary passage as an essential part of the total circulation, one through which all the blood returning to the vena cava from the arteries was propulsed into the left ventricle, distributed to the arteries, and so on, during life

In reading again recently the translation by Kenneth J Franklin of the *De Motu Cordis*,[11] I could not fail to evoke the names of Francis Bacon and Galileo who were his contemporaries and who may well be considered as the intellectual patrons of Harvey Of the former, he was the physician, to the teaching of the latter, he certainly attended during his student days in Padua [12]

Do I delude myself in considering that the method used by Harvey in his demonstration of the circulation was recognized by Bacon and appears as the sum of inductive and deductive reasoning continually controlled by experimentation? Not a single link is missing between the postulation, the affirmation and the demonstration, and for the demonstration he had recourse to all the resources of his imaginative mind, of his power of observation, of his amazing knowledge of the animal kingdom

From whom but Galileo could he have borrowed the notion of circular movement, of the kinetics of motion, of quantitative demonstration?

Nevertheless, the creator of hemodynamic thinking was not a respiratory physiologist R A Young in his Harveian Oratio of 1939 [13] may have made a

Fig 4 —A page from a manuscript in the Bibliothèque, Nationale, Paris, written probably around 1546.

dicates that he saw and read the original manuscript now at the Bibliothèque Nationale in Paris, then in the possession of the Landgrave of Hesse.

*William Harvey* Thus, Harvey, whose contribution to the discovery of the pulmonary circulation we shall now discuss, could not be accused of plagiarism on that account. Furthermore, he did not fail to acknowledge, in Chapter 7 of the *De Motu Cordis*,[11] the very skillful and learned anatomist, Colombo, who was "convinced of the truth . . . of the passage of blood through the lungs . . . from the size and structure of the vessels of the lungs, from

the fact that the vein-like artery and likewise the ventricle are always full of blood which must have come to them through the veins and by no other path than an intrapulmonary one." So much has been written about William Harvey during the past year and so well, that the task of discussing what is original, about his contribution to the description of the pulmonary circulation, is neither easy nor inspiring. I shall, however, try my hand and do it mostly in quoting relevant sentences translated from his celebrated book [11]

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gallant effort to show that Harvey was concerned with the interrelation between respiration and circulation Indeed, one can read in the *Praelectiones* that "life and respiration are convertible terms," and in marginal note of the same *Praelectiones* the question, "Why and how air is needed by animals *which breathe? and also air is necessary to a candle and to a fire . . ." It* is true also that in a letter dated 1651, he modified his views on the cooling effect of the respiration upon the blood Nonetheless, his views on respiration still remained those of Galen; and if he had some doubts, they could not be dispelled in his time for lack of proper chemical knowledge

In concluding this too brief account of the role of Harvey in the elaboration of the concept of the pulmonary circulation, I shall finally comment that he suspected that minute vessels could be found connecting the arteries with the veins, thus closing the circle With regard to the lungs, he speaks of the blood becoming diffusely distributed within the porosities of the lung parenchyma Four years after his death, the last link, the capillaries, were discovered

*Marcello Malpighi.* With Malpighi we meet a physiologist who applied a new technical device, the microscope, to many physiological problems and exhibited in his studies not only an unusual technical ability but also a considerable amount of ingenuity in the experimental design While holding the chair of Theoretical Medicine at the University of Pisa, he formed a close friendship with Borelli, a member of the famous Accademia del Cimento, a mathematician who had become interested in physiology, which according to him constituted a branch of physics To this famous man he addressed, in 1661, two memorable letters,[14] a recent translation of which we owe to James Young[15] In these letters Malpighi "put a few little observations that might increase the things found out about the lungs " These "little observations" *were no less, no more, the first description of the air sacs in the lungs of a* dog, and of the pulmonary capillaries of tortoise and frogs, "the whole race" of the latter, he jokingly claimed to "have almost destroyed " We may well admire the technical ability and the ingenuity which he displayed in observing with his microscope the movements of the blood in the tiny vessels of living frogs while the heart was beating, and in examining after ligature of the pulmonary veins their extirpated lungs, turgid with blood and dried in that state

In closing this fascinating chapter, may I point out another irony of fate The letters addressed by Malpighi in the most humble way to his friend, whose "authority and contrivance" he believed "would bring truth and dignity" to his observations, *brought to the sender everlasting fame.* The concept of iatromechanics in physiology, of which Borelli became an exponent, is now completely discarded and never led to any discovery[16]

### The Function Served by the Pulmonary Circulation

The true object served by pulmonary circulation is our next concern. We have noted earlier the persistence until Harvey's death of the antique belief that breathing cooled the blood and that the inspired air supplied the arterial blood with something undefined but essential to the maintenance of life This "something" was not isolated until the end of the eighteenth century. But

during the years immediately following Harvey's death, a famous British scientist, Robert Boyle, with the technical help of his brilliant assistant Robert Hooke, demonstrated experimentally that some substance in the inspired air was essential to life [17,18] Robert Hooke furthermore, after inventing the first artificial ventilator, was able to maintain life in dogs by insufflating air into *their lungs, held inflated and motionless by an ingenious contrivance.*[19] He demonstrated thereby that respiration was not dependent essentially on the movements of the lung.

*Richard Lower* Inspired and advised by Hooke, Richard Lower, a native of St Tudy in Cornwall, repeated these experiments and extended their significance. The account of his experiments on the dogs with open chest were published in *1669* in his book *Tractatus De Corde* [20] Of this book, Flourens[5] has said that it is "short, full, excellent"; of Lower himself that "he is one of the finest minds ever devoted to physiology," and I may add, in unison with J F Fulton,[21] the first of many distinguished Oxford physiologists The proof was given by him beyond any doubt that the function of the pulmonary circulation is the arterialization of the venous blood. This, Lower established by observing the change in the color of the blood under the immediate influence of ventilation The experiments were many and conclusive They were based on the maintenance or withdrawal of artificial ventilation, the closure or the opening of the trachea, the collapse and re-expansion of the lungs, the transfusion of venous blood through the ventilated lung of a dog recently killed

*Joseph Priestley* One hundred and fifteen years later, a British parson, Priestley, the creator of gas chemistry, explained the change of color in the blood by assuming that the venous blood contained a mysterious principle, the phlogiston, which on reaching the lungs was changed to the dephlogisticated air of the arteries In the spring of *1771* he had isolated the principle, present in the common air, which caused this transformation, but mistook it for laughing gas Shortly thereafter, on *March 8, 1775,* he had effectively produced oxygen by heating mercury red oxide and demonstrating it to be "better" than common air in sustaining life in mice However, "his blind adherence to the phlogiston theory in spite of his own effective discovery of oxygen . . shows the hold that one conceptual scheme may have on the mind of one investigator "[22] With all the facts at hand, Priestley was not able to give a correct interpretation of the phenomenon of respiration, and to solve the riddle of combustion by demonstrating that oxygen was a constituent of the atmosphere

*Antoine Laurent Lavoisier* This achievement, one of the decisive steps in the history of biological and chemical sciences, is to the credit of the French chemist, Lavoisier His research, pursued in twenty short years between *1772* and *1792,* built the foundation of modern chemistry To be sure, in recognizing in the atmosphere both an active gas and an inert one, he received directly or indirectly valuable hints from Priestley, benefiting also from "the improvement in communication among scientific men, which made science more and more of a co-operative effort "[22] In *May 1777,* Lavoisier communicated to the Académie des Sciences the results of accurate and convincing observations

which demonstrated the complete analogy between respiration in animals and chemical combustion.[23]

"On one hand," he wrote, "*the eminently respirable air is absorbed* (during inspiration) and on the other, the lungs give off the chalky aeriform acid ($CO_2$), equal in volume."

In the same report, he suggested that the red color of the blood was due to the "combination of the respirable gas (oxygen) with an animal liquor!" In *1780, in collaboration with Laplace, the future author of the Celestial Mechanics,* he created precise calorometric methods; from them they concluded, "Respiration is a combustion taking place in the lungs, the heat resulting from it is communicated to the blood and by it to the entire animal system."

*It is only in 1837,* and *1843,* that Gustav Magnus,[24] by comparing $O_2$ and $CO_2$ in the arteries and veins assigned to the body tissues their proper role in combustion and dispelled the error made by the French scientists.

Although tempted to elaborate on the circumstances of the brilliant life and epoch-making scientific output of Lavoisier, I shall cut short, as indeed did the guillotine set in motion by Coufinhal, the president of a revolutionary tribunal who, during the Terror, sent him to his death at the age of 50, with the alleged remark that "The Republic has no need for scientists." Times have changed!

To conclude the chapter of the arterialization of the blood we have to wait for the discovery of hemoglobin by Otto Funke in *1851;*[25] for the observation by Lothar Meyer, in *1857,*[26] that oxygen is not held in simple solution, and finally for the demonstration of the loose combination of oxygen with hemoglobin by Hoppe Seyler in *1861.*[27]

## The Earliest Acquisition Concerning the Dynamics of the Pulmonary Circulation

We now reach the middle of the nineteenth century. Under the leadership of Magendie, physiology had freed itself from the hold of metaphysical concepts, and at last was developing experimental methods and instrumentation based on sound scientific principles.

*Carl Ludwig.* In his Frankfurt laboratory, Carl Ludwig, in adding a float (*1847*) to the U mercury manometer developed by Poiseuille in *1828,* had perfected a unique tool which enabled the circulating blood to record its own mean pressure. Shortly thereafter, in *1852,* his pupil, Beutner[28] recorded pressure in the pulmonary artery of dogs. This preparation required the opening of the chest and the insertion of a canula after ligation of one of the two main branches of the pulmonary artery. From his measurements it immediately became apparent that the blood pressure in the pulmonary circulation was much lower than that in the systemic circulation. This, experimentally, confirmed the hypothesis advanced in *1733,* by Stephen Hales,[29] namely that on the basis of the respective thickness of their muscular walls, it could be deduced that the right ventricle had to do less work in order to eject blood into the pulmonary circulation than the left ventricle had to do in order to eject the same quantity of blood into the aorta. Among many other proofs of

the genius of the clergyman of Teddington, I may recall also at this time, that he measured, by direct observation, the rate of blood flow in the pulmonary capillaries of the frog and had suggested that the blood must traverse the lungs with "vastly greater rapidity than through other parts of the body."

*Auguste Chauveau and Jules Marey* Let me turn now to the early story of another tool, the cardiac catheter, which enabled two French physiologists, Chauveau and Marey, to measure blood pressure in the pulmonary circulation of *an intact* animal Since I have acquired prejudice regarding this tool, my account may well be somewhat lengthy.

Chauveau, Professor of Veterinary Medicine in Lyons, in *1856*, in collaboration with Faivre,[30] had measured mean pressure in the pulmonary artery of the horse with a trocart and found it to be half that in the carotid artery He knew well that the heart rate in this full-grown animal is very slow (from 30 to 40 pulsations per minute) which facilitated observations of the contraction of each chamber Marey was a young and brilliant Parisian physician, who subscribed enthusiastically to the then growing concept that experimental physiology is one of the keys to the understanding of pathological phenomena He had already devised instruments for the graphic registration of biologic phenomena They both joined their efforts in order to settle a long controversy concerning the cause and timing of the cardiac apex beat [31] It is not known, nor does it matter, which of the two associates suggested the introduction, by way of a peripheral vein (in this case the external jugular), of a catheter within the right heart cavities of an intact unanesthetized horse. Nor can we gather from their publications who designed the double lumen catheter (fig 5) with its two distal orifices 12 cm apart (For the purpose of comparison, the double lumen cardiac catheter used now in human subjects is illustrated in figure 6 )

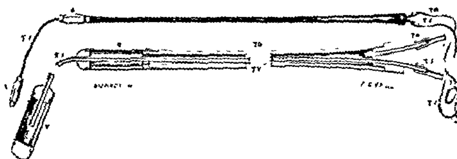


FIG 5 —The double lumen cardiac catheter constructed by Chaveau and Marey.

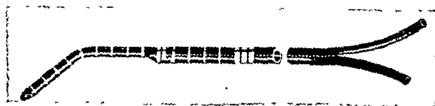


FIG 6 —Double lumen cardiac catheter in use in human subjects.

After connecting the two proximal orifices of the air-filled catheter, with an appropriate manometric device, also air-filled, Chauveau and Marey registered simultaneously the pressures which develop within the right auricle and ventricle during the cardiac cycle By modern standards, acceptable records of right intra-auricular and ventricular pressure pulses (fig 7) were simul-

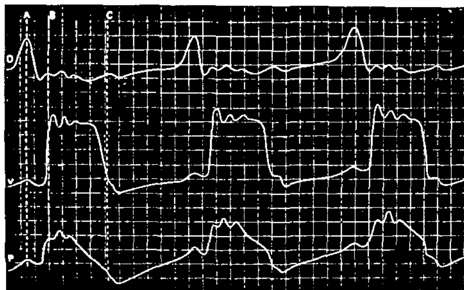



Fig. 7 —Simultaneous recording of blood pressures in the left atrium and right ventricle and of the apical beat

taneously secured while the cardiac apex beat was recorded through a manometric capsule inserted within an intercostal space Analysis of these tracings enabled them to demonstrate that the beginning of the apex beat coincides with the early systolic rise in the right ventricle after the auricular systolic wave was completed In order to make their demonstration even more convincing, they also performed the first recorded cardiac catheterization of the left ventricle by the arterial route For this purpose they developed a special catheter with which they secured pressure pulse tracings of the left ventricle simultaneously with pressure pulses in the right heart cavities and with the apex beat (fig 8)

Before leaving the subject of cardiac catheterization in the horse, I should like to make several further comments

First, the average figures given for right atrial, right ventricular and left ventricular systolic pressures were respectively 2 5, 27 0 and 128 0 mm Hg; these figures are remarkably consistent with those obtained more recently in dog and in man, using our present more accurate methods

Second, the safety of the technique was emphasized. For the sake of the worrying physicians, and also of the antivivisectionists, I am quoting a footnote in the book, *La Physiologie medicale de la circulation du sang*, written by Marey in *1863:* [32] "One can be assured of the harmlessness of this method by examining the horse, who is least disturbed, walks and eats as usual In

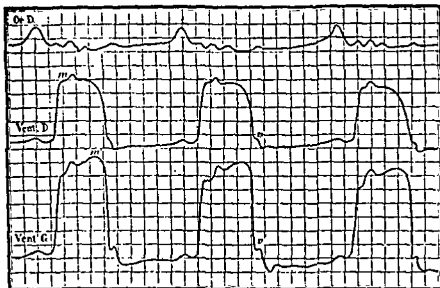



FIG 8 — Simultaneous recording of blood pressures in the right atrium and right and left ventricles

only a few instances, is the pulse rate slightly increased, especially at the time of the introduction of the catheter within the heart cavities."

To these comments, I should like to add a note of wonder: Why is it that Marey, who, in the preface of the book to which I have just referred, emphasizes the importance, in physical examination, of extending the limits of our senses, and lists many human cavities and canalicular systems which may be explored with catheters and specula? Why is it that he did not extend his new experimental method to the exploration of the circulation in man?

In the second part of the last century, it was also realized that measurements of pulmonary artery blow pressure are not all that counts in the study of the dynamics of the pulmonary circulation Thus, before concluding, I should like to speak briefly of two physiologists, Fick and François-Franck, who played a considerable role in the furthering of our knowledge of the dynamics of the pulmonary circulation; the former by enunciating a principle of far-reaching importance in its application to the measurement of pulmonary blood flow, the latter by demonstrating that the autonomic nervous system is capable of causing pulmonary vasoconstriction in the experimental animal

*Adolph Fick* Shortly after his promotion to Professor of Physiology at the Hochschule of Wurzburg, this versatile scientist presented, in *1870*, a brief and now famous note before the Society of Physiology and Medicine of this university town (fig 9). It is entitled *Ueber die Messung des Blutquantums in den Herzventrikeln*[33]—a rather misleading title for us today, unless it is assumed that there is no residual volume in the ventricle after systolic ejection!

A period of 16 years elapsed before the Fick principle was applied to the

Sitzungsberichte für das Gesellschaftsjahr 1870.

## XIV. Sitzung am 9. Juli 1870.

**Inhalt: Fick:** Ueber die Messung des Blutquantums in den Herzventrikeln. — **Rinecker:** Ueber Rötheln und Masern.

1) Das Protokoll der letzten Sitzung wurde verlesen und genehmigt.
2) Neu eingelaufene Bücher werden in Vorlage gebracht.
3) Hr. Dr. phil. Röntgen wird als Mitglied angemeldet.
4) Hr. Fick hält einen Vortrag über die Messung des Blutquantums, das in jeder Systole durch die Herzventrikel ausgeworfen wird, eine Grösse, deren Kenntniss ohne Zweifel von grösster Wichtigkeit ist. Gleichwohl sind darüber die abweichendsten Ansichten aufgestellt. Während Th. Young die in Rede stehende Grösse auf etwa 45ccm anschlägt, cursiren in den neueren Lehrbüchern der Physiologie meist sehr viel höhere Angaben, welche, gestützt auf die Schätzungen von Volkmann und Vierordt, sich bis auf 180ccm belaufen. Bei dieser Sachlage ist es seltsam, dass man noch nicht auf folgenden naheliegenden Weg gekommen ist, auf dem diese wichtige Grösse wenigstens an Thieren direkter Bestimmung zugänglich ist. Man bestimme, wie viel Sauerstoff ein Thier während einer gewissen Zeit aus der Luft aufnimmt und wie viel Kohlensäure es abgibt. Man nehme ferner dem Thiere während der Versuchszeit eine Probe arteriellen und eine Probe venösen Blutes. In beiden ist der Sauerstoffgehalt und der Kohlensäuregehalt zu ermitteln. Die Differenz des Sauerstoffgehaltes ergibt, wie viel Sauerstoff jedes Cubiccentimeter Blut beim Durchgang durch die Lungen aufnimmt, und da man weiss, wie viel Sauerstoff im Ganzen während einer bestimmten Zeit aufgenommen wurde, so kann man berechnen, wie viel Cubiccentimeter Blut während dieser Zeit die Lungen passirten, oder wenn man durch die Anzahl der Herzschläge in dieser Zeit dividirt, wie viel Cubiccentimeter Blut mit jeder Systole des Herzens ausgeworfen wurden. Die entsprechende Rechnung mit den Kohlensäuremengen gibt eine Bestimmung desselben Werthes, welche die erstere controlirt.

Da zur Ausführung dieser Methode 2 Gaspumpen gehören, so ist der Vortragende leider nicht in der Lage, experimentelle Bestimmungen mitzutheilen. Er will daher nur noch nach dem Schema der angegebenen Methode eine Berechnung der Blutstromstärke des Menschen geben, gegründet auf mehr oder weniger willkürliche Data. Nach den von Scheffer in Ludwig's Laboratorium ausgeführten Versuchen enthält 1ccm arterielles Hundeblut 0,146ccm Sauerstoff (gemessen bei 0° Temperatur und 1m Quecksilber Druck), 1ccm venöses Hundeblut enthält 0,0905ccm Sauerstoff. Jedes Cubiccentimeter Blut nimmt also beim Durchgang durch die Lungen 0,0555ccm Sauerstoff auf. Nehme man an, das wäre beim Menschen gerade so. Nehme man ferner an, ein Mensch absorbirte in 24h 833gr Sauerstoff aus der Luft. Sie nehmen *bei 0° und 1m Druck 433200ccm Raum ein. Demnach würden in den Lungen des* Menschen jede Secunde 5ccm Sauerstoff absorbirt. Um diese Absorption zu bewerkstelligen, müssten aber der obigen Annahme gemäss $\frac{5}{0{,}0555}$ ccm Blut die Lungen durchströmen, d. h. 90ccm. Angenommen endlich, dass 7 Systolen in 6 Secunden erfolgten, würden mit jeder Systole des Ventrikels 77ccm Blut ausgeworfen.

Fig 9—Photographic reproduction of the proceedings of the Society of Physiology and Medicine of Wurzburg (*July 9, 1870*)

measurement of blood flow in the experimental animal At last, in *1886* Grehant and Quinquaud [34] made use of a cardiac catheter, introduced by the venous route, to secure samples of mixed venous blood from the right heart of

dogs. The long delay between the enunciation of a principle and its experimental application is the more surprising since Badoud,[35] an assistant of Fick, in 1876, used a long glass catheter with a curved tip, which he introduced in the external jugular vein, not in order to secure mixed venous blood but in order to record pressures in the pulmonary artery of dogs! Apparently the Würzburg laboratory still lacked the two gas pumps needed for the extraction of gas from the blood, the inavailability of which pumps was deplored and cited by Fick, when in his note of *1870* he explained why he could not supply his own data for the calculation of the stroke volume in the dog

*Charles François-Franck* The role of the autonomic nervous system in the regulation of the pulmonary, was much debated in the *1880's* and in English-speaking countries the name of Bradford and Dean[36] is usually associated with the earliest experiments (*1889*) concerning the problem. Apparently, these English workers were unaware of the earlier work of François-Franck, presented at meetings or published from *1880* on.[37] In two papers published by François-Franck in *1895*,[38] in order to sustain his claim for priority in this matter, one can find how well aware François-Franck was of the special problems encountered in investigating the pulmonary vasomotor system. Thus he emphasized the difficulties related to the intervention of the heart action, and to the back effects upon the pulmonary vessels of the direct or reflex action of the autonomic stimuli on the systemic circulation. According to him, the only valid demonstration of the vasoconstrictor action on the pulmonary vessels, resulting from stimulation of the first dorsal sympathetic ganglion, resides in *the elevation of pressure in the pulmonary artery immediately followed by a drop of pressure in the left atrium* Such a demonstration, states François-Franck, has been given in the thesis of his pupil, Dr. Lalesque, published in Paris by G Masson in *1881* In the introduction of the first of these two remarkable papers, one will also find the following comment, which could well have been written seventy years later "In spite of many reports since Brown-Sequard became interested in the problem, there is still some doubt among physiologists as to the exact influence of the sympathetic system upon vasomotricity of the pulmonary vessels "

## CONCLUSION

In his *Introduction to Experimental Medicine*, Claude Bernard has upheld, without reservation, the Positivist thesis that Science today being necessarily superior to the science of the past, it is of no avail to look for progress in the knowledge of the past To my mind, such an attitude involves a dogmatic concept of science and is created by the mirage of a final state of knowledge

Looking backward has reinforced my belief in the temporary and relative character of the successive "truths" I have called up before you some men in search of this elusive absolute, sustained by their faith, by their logic and by the results of their experience Indeed, scientists of all times built concepts to be denied by new techniques, new experiments and their interpretations, leading to improved or modified concepts, thus turning in a circle which never ends.

I have also found, among other ethical values, an incentive for greater

tolerance and for the admission of one's error. Last, but not least, I have recognized in the men searching for truth the tension of their anxiety created by the ambivalent nature of the Western man who in his quest cannot escape a continuous doubt of his certainties. In this paradox, one may find the mainstay of our Christian civilization and our hope for its survival.

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# II. THE PHYSIOLOGY OF THE PULMONARY CIRCULATION

CHAIRMAN: JULIUS H. COMROE, JR.
CO-CHAIRMAN: GEORGE E. WAKERLIN

## *Functions of the Pulmonary Circulation*

*By* JULIUS H. COMROE, JR.

THE PRIMARY FUNCTION of the pulmonary circulation is gas exchange The functional parts of the pulmonary circulation are the pulmonary capillaries Therefore, it seems proper for me to direct your attention first to the capillary bed

True, there is also a blood pump, the right ventricle, which does the work of pushing mixed venous blood along the capillaries True, there are resistances to flow, both normal and abnormal, in the arterioles and at valvular orifices True, there are regulatory mechanisms which partly control the pump and the resistances But these *really* exist to serve and to protect the pulmonary capillary bed

The pulmonary capillaries are pictured in figure 1, as conceived by William Snow Miller [1] (A) and as photographed by Low,[2] using the electron microscope with a magnification of 25,000 times (B) We see an almost continuous sheet of pulmonary capillaries except for the spaces where alveoli come into intimate contact with them We see also that the "membrane" separating gas from blood is extremely thin (less than 0 1 micron) but that it is in fact two membranes—one alveolar and one capillary In health these are so closely applied to each other that the diffusion distance for gases is very small; however, there is a potential space between them and this can be filled with transudate, exudate or fibrous tissue

The volume of blood contained within the pulmonary capillaries is small, *about 75 ml in a normal adult* (This capillary blood volume must not be confused with the total pulmonary blood volume which is about 10 to 15 times greater ) But it is spread in a thin sheet with a very large area, estimates of this area vary from 30 to 50 sq M. The diffusing capacity of the alveolar capillary membranes is not really a fixed "capacity" since it can increase when pulmonary blood flow increases, as in muscular exercise, either because of dilatation of functioning capillaries or opening of new channels or both: approximately 30 to 50 ml of $O_2$ can pass across the membranes per minute for each mm Hg pressure gradient of $O_2$ [3]

Pressure and resistance to flow are low in the pulmonary capillary and must remain low in health in order to prevent transudation of fluid across the capillary wall into the intermembranous space or into the alveoli. The volume flow of blood through the capillaries is great (normally about equal to the cardiac output) and there is a decided volume pulse in the capillaries, at least when the precapillary resistance is normal[4]

Normally the mixed venous blood is distributed evenly to all of the pulmonary capillaries (or at least in relation to the alveolar ventilation of each area) We have been so intent on obtaining precise measurements of the quantity *of alveolar ventilation and pulmonary blood flow that we occasionally* forget that ventilation and blood flow need not be normal just because their *volume* per minute is normal It is well known that uneven ventilation causes arterial anoxemia; it is less well known (or remembered) that uneven capillary blood flow also causes anoxemia Non-uniformity of capillary blood flow is more difficult to detect and quantitate than uneven ventilation; its precise measurement still represents a challenge to investigators[5] It is likely that capillary blood flow may adjust to uneven alveolar ventilation so that poorly ventilated areas receive less blood for arterialization and well ventilated areas receive more capillary blood

Vesalius, in *1513*, 10 years before Michael Servetus' account of the pulmonary circulation, was "driven to wonder at the handiwork of the Almighty by means of which the blood sweats from the right into the left ventricle through passages which escape human vision " We know now that blood does *not* sweat through the intraventricular septum, but, in health, passes right to left through the pulmonary circulation We know now that later misconceptions were also false.

The pulmonary circulation is *not* a lesser circulation, for it has a greater blood flow than any other organ

It is *not* always a low resistance, low pressure system Physiologically, it is a high resistance, high pressure system in the fetus and until the first breath or two in neonatal life, pathologically, it can become a high resistance, high pressure system in response to long-continued increased flow or pressure or obstruction and this can revert back to or toward a low resistance, low pressure system upon relief of the abnormality

It is *not* devoid of smooth muscle It is there and it can both hypertrophy and regress

It is *not* lacking in vasomotor regulation although this appears to be excited by stimuli different from those which excite the peripheral systemic circulation

Many things we do not know The purpose of this conference should be to direct attention to areas of ignorance Some of these are.

What is the function of all of the sensory end organs and paraganglia attached to small and large pulmonary vessels? Do changes in pressure or resistance to flow lead to the sensory experience of pain?

Why should the injection of a few micrograms of certain chemical sub-

stances into the pulmonary circulation cause reflex bradycardia, periph systemic vasodilatation, system arterial hypotension and apnea?[6] (See fig

Why are white blood cells, under certain experimental conditions, trap

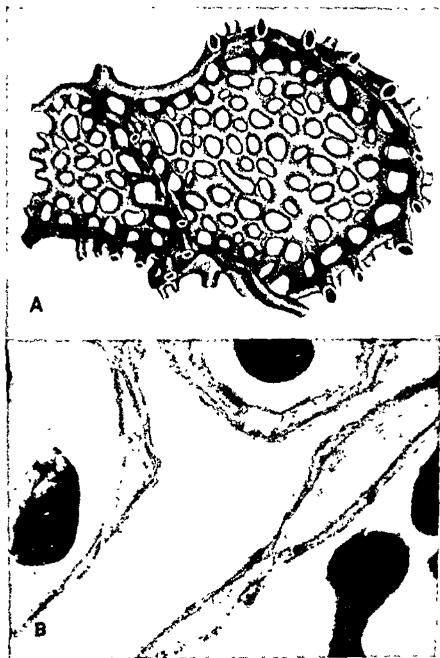



FIGURE 1

A. Miller's concept of the pulmonary capillary bed.[1]

in the pulmonary vascular bed? Is this circulation, accidentally or by design, a filtering mechanism for mixed venous blood? How do the pulmonary tissues react to trapped particles? What do irritant gases or intravascular particles do to the pulmonary circulation, regionally and generally?

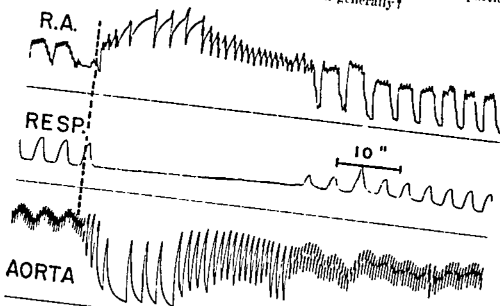



Fig 2—Bradycardia, hypotension and apnea following the injection (at dotted vertical line) of serotonin into the pulmonary artery of a cat[6]

Why is the lung rich in heparin, histamine and certain enzymes? Does the lung have any significant metabolic rate? Does it produce any chemicals with significant local or remote action?[7]

Are the pulmonary capillaries always open? Do they alternate? Is there significant resistance to flow in the capillary bed? What are the limits to capillary distensibility? Does any part or the whole of the pulmonary circulation act, accidentally or by design, as a blood reservoir?

Can we detect early changes in membrane thickness, area, diffusing capacity, capillary blood volume or uniformity of blood flow before disease is far advanced?

What is the stimulus to pulmonary arteriolar constriction in response to anoxia, increased $P_{CO_2}$ or heightened left atrial pressure? What is the time course of vasoconstriction, or smooth muscle hypertrophy and of vascular sclerosis and of their regression, if reversible?

What is the stimulus to right ventricular hypertrophy? What is the time required for hypertrophy and its reversion to normal? Why and when does hypertrophy lead to failure?

It is urgent that we confess to and emphasize areas of uncertainty and ignorance and open our physiological, pathological, surgical, cardiological or

radiological minds to new thoughts, concepts, and methods of each of these disciplines. In this regard, I recommend that you think seriously of the moral of the old Hindu fable of the blind men and the elephant:

THE BLIND MEN AND THE ELEPHANT

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The FIRST approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl.
"God bless me! but the Elephant
Is very like a wall!"

The SECOND, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The THIRD approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake
"I see," quoth he, "the Elephant
Is very like a snake!"

The FOURTH reached out an eager hand,
And felt about the knee,
"What most this wondrous beast is like
Is mighty plain," said he,
"'Tis clear enough the Elephant
Is very like a tree!"

The FIFTH, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an Elephant
Is very like a fan!"

The SIXTH no sooner had begun
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant

And so these men of Indostan
  Disputed loud and long,
Each in his own opinion
  *Exceeding stiff and strong,*
Though each was partly in the right,
  *And all were in the wrong!*

MORAL

*So oft in scientific wars*
  The disputants, I ween,
Rail on in utter ignorance
  Of what each other mean,
And prate about an elephant
  Not one of them has seen!

*John Godfrey Saxe*

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# The Relation Between Pressure and Flow in the Pulmonary Bed

*By* Alan C. Burton

It has taken us more than 10 years in our laboratory to reach the point where we feel that we understand the general relation, in a variety of vascular beds, between pressure and flow. Our experience has been mainly with peripheral vascular beds, and we have only a very small amount of data on the pulmonary circulation However, it may be useful to summarize, very sketchily indeed, our knowledge and understanding of the factors that determine the shape of the curves of flow versus pressure *in general,* and then discuss how important or not these factors may be in the pulmonary vessels After all, at the moment it is not lack of data that is hampering all of us, but lack of understanding of the mass of experimental data already at hand, on the interpretation of which there is very little agreement

*Water Flowing in Rigid, Nondistensible Tubes*

Whenever flow is streamlined, not turbulent (and this is the case in most of the circulation), the flow is proportional to the driving pressure, by Poiseuille's experimental law, later developed from Newton's theory of viscosity by Hagen

$$F = \Delta P \times \left(\frac{\pi}{8}\right) \times \left(\frac{1}{\eta}\right) \times \left(\frac{r^4}{\lambda}\right)$$

When F is the flow in ml /sec , P is the pressure drop down the tube, $\frac{\pi}{8}$ is a '*numerical factor,*' originating in the integrations in Hagen's development, $\frac{1}{\eta}$ is the *viscosity factor* in Poises, and $\frac{r^4}{\lambda}$ is the '*geometrical factor* ' The flow-pressure curves are then straight lines through the origin and the resistance to flow, defined as the ratio of driving force P to the flow F, is given by.

$$R = \left(\frac{8}{\pi}\right) \times \eta \times \left(\frac{\lambda}{r^4}\right)$$

The resistance is a constant for a given tube and viscosity, and does not vary with the rate of flow or the pressure Also, for fluid of a normal viscosity (a Newtonian fluid) the viscosity is independent of the other variables, such as the rate of flow, the pressure, or the size of the tube.

*Flow of Blood in Vascular Beds*

In very great contrast the flow-pressure curves with blood in vascular beds are quite different. The differences are.

1. The curves do not pass through the origin, and flow is not appreciable until a critical pressure is reached, called by us the critical closing pressure (C.C.P.). This C.C.P. rises as the vasomotor tone increases, when the increase of tone is produced experimentally by perfusion with vasoactive drugs or by nerve stimulation.

2 Although the curve for very dilated vessels is almost linear, with increasing tone the curves become sigmoid and finally very convex to the flow axis

3 At sufficiently high pressures the curves tend to become straight lines pointing to the origin.

4 The resistance is almost constant at high pressures, but rises as the pressure is reduced, to reach very high values, rather abruptly, near the C C P

Of course, I have had to gloss over differences in specific vascular beds for the sake of brevity For example, in some cases, although an abrupt rise of resistance at a critical pressure indicates that many vessels have closed, others (shunts) remain open so the curves of flow do reach the origin, and the resistance, although it rises abruptly, does not rise to infinity. In other cases, notably the kidney, the resistance actually increases at high pressures, probably due to a reflex.

*Why these Differences?*

Two possible explanations are advanced The first is that blood has anomalous viscosity, so that the viscosity factor of Poiseuille's equation is a function of the rate of flow, and hence of the driving pressure This is thought by many to be the main factor and is so described in some textbooks and authoritative reviews We now know this is very far from the truth, since last year Dr R H Haynes in our laboratory succeeded in elucidating quite completely the mechanism of the anomaly in the viscosity of blood The anomaly is due to axial accumulation of red cells, which indeed takes place However, the axial accumulation is complete, reaching a saturation value, and the effective viscosity no longer changes with pressure, at a rate of flow that is very small indeed in the range of physiological values Because of axial accumulation, the effective viscosity of blood is considerably less than it would be otherwise, but in the physiological range viscosity does *not* change appreciably with the rate of flow

Convincing proof that anomalous viscosity is a very minor factor indeed is provided by the following two facts

1 The flow pressure curves in vascular beds when a fluid of normal viscosity is used, such as Ringer's solution, are not straight lines through the origin, but practically identical in shape with those obtained when blood is used

2 The flow-pressure curves of blood in rigid, nondistensible tubes are quite unlike those found in distensible vascular beds, but almost linear when the flow exceeds a very small amount which is below the physiological range

The second explanation possible is that the geometric factor in Poiseuille's law is not a constant but depends on the pressure, i e the difference is due

to the *distensibility* of blood vessels This turns out to be the major factor Indeed, assuming the right kind of distensibility in the wall of blood vessels, where the resistance to stretch increases as it is stretched more (this is due to the combination of elastic and collagenous fibres in the architecture of vessels), and the existence of *smooth muscle contraction, relatively independent* of the degree of stretch (active tension), we have been able completely to explain, not only the C C P., but also the succession of shapes of these non-linear flow-pressure curves It is simply a matter of setting up the equations for the physical equilibrium of a cylinder under these conditions.

In searching for the factors that affect flow-pressure relations in the pulmonary bed therefore, we can omit, almost completely, anomalous viscosity and concentrate on the effects of distensibility, and of the active tension of *contraction of smooth muscle in the vessel walls, if this exists in the lungs*

### *Is there Vasomotor Activity in the Pulmonary Resistance Vessels?*

Can there be in pulmonary vessels considerable active tension causing critical closure in the pulmonary bed, and helping to make flow-pressure curves *of the shapes shown? The histology books are remarkable reticent on the* existence of much smooth muscle in the walls of the small pulmonary vessels While the literature contains considerable indirect evidence of an increased resistance when vasoactive drugs were perfused, it is not always possible to exclude a passive decrease in diameter due to a change in the pressure, i e due to distensibility Dr Patel and I wanted more direct morphological evidence on this point By making plastic casts of the pulmonary bed, by the method of Essex, and examining the fine endings of these, which are as small as *10 microns in diameter, we became convinced there was ample smooth* muscle to cause very great vasomotor tone if it were stimulated to contract[1] The casts of two sides of a lung were markedly different if one side were perfused with noradrenalin up to the moment of injection of the plastic The small vessels on this side were no longer relatively smooth and cylindrical, but *contorted,* and scored by helical grooves, appearing like a "gnarled" branch of an old apple tree We developed a 'gnarly' index from a microscopic examination of 100 small endings of each cast, by a blind technique (the *observer did not know the origin of what he examined) The results show,* with statistical significance, that there can indeed be active constriction in the small pulmonary vessels The activity was greater in the vessels less than 25 microns in diameter, than in larger vessels, at least for small concentrations of the active drug We are sure, therefore, that there can be a high C C P. in the pulmonary bed, although we do not know in what physiological or pathological conditions active constriction may occur

Now we have never seen a C.C.P. in mammalian peripheral vascular beds, *less than 10 mm Hg, even in very dilated vessels* We attribute this residual C.C.P. to an interfacial tension between blood and the wall, since only detergent agents remove it. We think, therefore, that the C C P in the lungs must at least be 10 mm.Hg, and may, under vasomotor tone, *be much greater* The pressure in the pulmonary artery available to keep the small vessels open is

so small that the vessels of the upper lobes, in the erect posture, must be very close to closure, especially in expiration For example, if my pulmonary arterial pressure is 25 mm Hg, and the hydrostatic factor $\rho$ gh for the top of my thorax amounts to subtracting 15 mm Hg, very little is left to keep the uppermost vessels open Perhaps there is some clinical evidence of the operation of this factor, since, I am told, in cases of pulmonary hypotension, necrosis appears in the upper lobes first

*The Role of Distensibility, the Transmural Pressure*

I have deliberately slid over an important point, which escaped me for some years, during which time my *thinking was still quite confused The pressure* that determines the size of a resistance vessel, with a given distensibility and vasomotor tone, is *its transmural pressure This is the difference between the* intravascular pressure of the blood inside it, and the tissue pressure outside it. *We introduced the term some years ago, and it has been a great help to our* thinking [2] I am delighted to see how many others are now employing the term *and the concept*

As soon as it is realized that the transmural pressure of the resistance vessels *is not necessarily related directly to the pressure drop from artery to* vein, it becomes apparent how meaningless it is to talk about the flow-pressure *curve of a vascular bed, or even about a single family of curves for different* degrees of vasomotor tone For example Usually, one obtains a flow-pressure curve by lowering successively the *arterial* or *perfusion* pressure, while the venous or *outflow* pressure is kept constant When this is the procedure, the transmural pressure of the resistance vessels decreases as the arterial pressure is lowered (It is easy to prove that if most of the total resistance to flow resides in a particular set of vessels, as it does in the arterioles in the peripheral circulation, the average pressure in these vessels will be midway between arterial and venous pressure ) On the other hand, we might decide to obtain the flow-pressure curve by keeping the arterial pressure constant, while successively raising the venous pressure In this case, the T M P would increase as the pressure gradient fell, and we would expect to get a quite different *shape of flow pressure curve Miss Rosenberg and I* [3] *have shown this experi*mentally for the perfused rabbit ear, and recently Levy has published a paper [4] in which he announces the same discovery for the hind limb of dogs Levy suggests a rather complicated explanation in terms of differential distensibility of different vessels, or a reflex, but in terms of the T M P of the resistance vessels, the explanation is very simple

We must think, therefore, of an infinite number of flow-pressure curves for any vascular bed For variations of vasomotor tone there is a family of curves, and for each condition of the transmural pressure of the resistance vessels *there is another family of such curves For example,* using the conventional method of reducing the driving pressure by lowering the arterial pressure, keeping the venous pressure constant, we will find a different flow-pressure curve for each value of the venous pressure

*The Transmural Pressure in the Pulmonary Resistance Vessels*

This consideration is of particular importance in the pulmonary bed, for the T M P of the small pulmonary vessels is profoundly affected by the changes of intrathoracic pressure during inspiration, or in the many experiments on flow-pressure relations made on isolated lungs Dr Patel and I spent *a considerable time reading the voluminous literature on the effects of the* degree of distension of the lungs on the pulmonary vascular resistance. As you know, there has been a violent controversy on this for over 30 years[1] One school is convinced that during inspiration the resistance increases (a recent paper is that of Helman et al[5] on humans), the other school finds the opposite The experiments are variously on animals with closed chests, with open chests, or with excised lungs mounted in a box. Measurements are of pulmonary artery pressure, blood flow (cardiac output), pulmonary vascular volume (Macklin[6]) and radiological shadows of these vessels. Sometimes the lungs *are inflated by positive-pressure inflation, i e by raising the intra*-alveolar pressure and not altering the outside, or 'intrathoracic pressure,' sometimes by *negative-pressure inflation,* i e. by lowering the intra-alveolar or outside pressure in the box The driving pressure is supplied either by the heart, by a pump, or by the head of pressure from a perfusion bottle Visscher[7] introduced a variant by putting the perfusion bottle inside the box so it shared in the reduction of pressure when using negative pressure inflation, feeling that this represented conditions in the intact thorax In view of this welter of experimental data, on which interpretation we apparently cannot agree, I suggest *that it would be a waste of time and effort to make any* more measurements of this kind, until we do agree on interpretation

In studying the literature, we made an astonishing discovery. It was that, in spite of the opposite conclusions in the many papers, there was no serious conflict of experimental results at all, as to what happened to the pulmonary artery pressure, to the *blood flow, and so on The conflict rests entirely on* the interpretation of the results in terms of pulmonary resistance, and arises because one school uses what is called the 'effective pulmonary artery pressure' in their calculation of resistance, the other uses (we think, correctly) the pressure gradient, i e pulmonary artery minus pulmonary venous pressure (although too often this latter was assumed rather than measured) The 'effective arterial pressure' is the actual arterial pressure minus the intrathoracic pressure Now the only way that this could be 'effective' would be in driving blood from inside to outside the pulmonary artery, if there were a hole in the wall The '*effective pressure' does resemble the transmural pressure of the pul*monary artery, and so can govern the size of that artery But it can have nothing to do with the driving force for the flow of blood down the line of pulmonary resistance As soon as we had corrected the interpretation of those who used 'effective pressure,' we had complete agreement, that in the normal respiratory cycle, *pulmonary resistance fell in inspiration and rose in expira*tion

However, Dr Patel and I did some experiments on opened-chest rabbits and on rabbit lungs, inflated by positive- or by negative-pressure inflation

It was a good thing we did, for we found there is more in the results than can be explained by the changes in transmural pressure, which will produce a change in size of the vessels by the usual mode of passive distension or passive contraction[8] The simple mathematical analysis is based on the statement that the tissue pressure in the lungs must be between the alveolar pressure and the intrathoracic pressure. The analysis shows that:

1 In positive-pressure inflation, the T M P of pulmonary vessels must decrease as the distending pressure is increased (this would increase the resistance).

2 In negative-pressure inflation (as in normal inspiration) the T M P. must increase as the distension increases (this would decrease the resistance)

3 When the perfusion pressure shares in the decrease in intrathoracic pressure in negative-pressure inflation, as in Visscher's experiments, the T M P decreases as the distention increases and resistance would increase. This is what Visscher found Note that in this case positive and negative pressure inflation produces the same result

Note that the effect on T M P does not depend only on the degree of inflation, but on how that inflation is produced There seems to have been a general assumption that for the same degree of inflation, however produced, the effect on the vessels would be the same This was a fallacy

The curves for positive-pressure inflation, either in the excised lungs or in the opened-chest animal, proved to be always U-shaped, with a minimum resistance at an inflation pressure of between 8 to 12 cm $H_2O$ The rise in resistance for higher positive-pressures of inflation was expected on the basis of T M P , the rise at lower pressures, i e in the lungs as they collapsed, was contrary to expectation The curves with negative-pressure inflation were as expected, and showed no hint of a U-shape, the resistance falling steadily as the lungs were distended Weil et al[9] also have recently found U-shaped curves of resistance with the use of positive-pressure inflation There is abundant evidence in humans that the vascular resistance rises greatly when lungs are collapsed, for in unilateral pneumothorax and in chronic atelectasis[10,11] there is very little drop in arterial oxygen saturation This must mean that blood flow through the collapsed lungs is very slight To what can we attribute this increase in resistance as the lungs collapse? We think it is a mechanical effect of distortion or *kinking* of the small vessels Histologists have described this in the lung capillaries of collapsed specimens Our belief in this explanation was intensified when we found there was a similar increase in resistance of a length of small rubber tubing, cemented to the surface of a partially inflated balloon, when that balloon was allowed to collapse Evidently the geometry of the small vessels of the lung is adapted to a moderate degree of inflation, perhaps that of the normal expiratory position, and they are distorted on further collapse of the lung

However, there is some evidence that a reflex vasoconstriction is elicited when the lungs collapse We went back to the original data and enumerated the numbers of vessels that were scored as gnarled to different degrees in the casts made with the lungs inflated to different pressures The incidence of gnarliness was significantly greater in the low range of inflation pressure

(0 to 6 cm.$H_2O$) than for the moderate range (7 to 16 cm.$H_2O$). In contrast there was no significant difference for higher pressures, though resistance to flow again increased. Also, we found a more marked U-shape of the curves of resistance in the intact lungs than in those that were excised. Of course, we may have mistaken deformation and kinking of the vessels on collapse for gnarliness, but we feel that no external forces could produce the characteristic appearance when the helical bands of smooth muscle contract. Such a vasoconstriction could be the result of anoxia or of venous congestion, through a veno-vasomotor reflex.

We believe therefore, in spite of the contradictions of statements in the literature, that in negative-pressure inflation, as in normal respiration, it is established that the pulmonary resistance tends to fall. Those who, by the erroneous use of 'effective pressure,' concluded the opposite often quote the classical work of Cloetta[12] to support their view. Cloetta showed that the lung vessels contained less blood in what he thought was normal inspiration, i.e. negative pressure inflation. However, he simply clamped the trachea at the height of inspiration, and then opened the chest to fix the tissues for histological study. At the moment of opening the chest, the negative inflation pressure in the intrathoracic space would disappear, and the air trapped in the lungs would be compressed. Nothing could have prevented blood from leaving the lungs. What he studied represented the conditions in positive-pressure inflation, not negative-pressure inflation or normal inspiration. This illustrates the dangers of quoting classical papers without a very careful re-examination of their contents.

*Conclusions.* The hemodynamics of the pulmonary vascular bed must depend on the same factors as in peripheral beds, namely on the distensibility and the active tension in the walls of the vessels. Moreover, the transmural pressure undergoes complicated changes during the respiratory cycle. Also, a quite small degree of vasomotor tone might tend to close these vessels completely since the arterial pressure available to keep them open is much less than in the systemic circulation. The fact that the literature on the subject may appear to be "a tale told by an idiot, full of sound and fury, signifying nothing" is due to erroneous use of invalid concepts. In terms of T.M.P., the results of all workers fall into a consistent pattern. An added complication is an increase of resistance when lungs approach collapse, probably due to a mechanical kinking of the small vessels.

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## DISCUSSION

SARNOFF I would like to make one or two comments

Actually, the critical closing pressure of the lung to which Dr Burton referred has been estimated in the experiments with differential lung perfusion in the dog with an open chest under anesthesia, by the elegant experiments of Borst, MacGregor, Berglund and Whittenberger, published in *Circulation Research 1957* It was found to be somewhere in the vicinity of 6 0 cm of water The problem of apical flow is one that puzzles many of us, Dr. Burton

I had occasion two weeks ago, Mr Chairman, to visit with Dr Patel, Dr Burton's co-worker with the plastic casts he referred to, who is now at Salt Lake City I must say that his gross and microscopic observation of these casts is most convincing They certainly throw some light on a gnarly problem

I can't believe that there is any residual doubt at all about the fact that catechol amines when injected into the pulmonary vascular bed in the concentrations used do indeed cause substantial changes in the force of constriction of certain pulmonary vessels This is consonant with the observations on differential pulmonary flow by Borst, MacGregor, Berglund and Whittenberger, wherein the *unilateral* introduction of catechol amines produced a substantial increase in the resistance of that lung while the other lung, of course, had its resistance decreased passively

This brings up a point which, I believe, is very important to emphasize early in this symposium Many articles published in the medical literature reveal that the authors have apparently unwittingly equated changes in resistance and changes in the tone of the pulmonary vascular bed For example, some investigators will give hexamethonium, measure changes in cardiac output, pulmonary artery and sometimes pulmonary capillary or left atrial pressures, and then calculate resistances They then proceed to draw deductions concerning the effect of hexamethonium on the tone (force of contraction of smooth muscle) of the critical resistance elements in the pulmonary vascular bed Not infrequently, I believe, the deductions to be drawn, are diametrically opposed to those that are drawn I would like to give one example and indulge in some hyperbole better to emphasize the point

Let's examine the situation in which, because of an induced increase of the resistance to left ventricular inflow, the left atrial pressure, is, say, 40 cm. of water and pulmonary artery pressure is 50 cm of water. The $\Delta P$ is 10 and cardiac output is 5, the resistance is 10/5 or 2 After dilating the peripheral vascular bed, the pulmonary artery pressure falls to 15, and the left atrial pressure to 5, while the cardiac output is still 5, the $\Delta P$ is still 10, and the resistance is still 10/5 or 2 There is no change in resistance whatsoever, and some investigators will be induced, therefore, to think that there has been no functional change in the tone of the pulmonary vascular bed

Nothing could be more contrary to fact At a distending pressure of the pulmonary artery of 50 and the pulmonary veins of 40, the resistance vessels would be quite large; contrariwise, at 15 and 5 and without any change in tone of these vessels they would be smaller unless the system is a rigid one The fact that no change in resistance has occurred indicates evidence in favor of substantial pulmonary vasodilation (increased distensibility) even in the absence of any change in calculated vascular resistance In other instances, calculated resistance can go up while tone is decreasing, and vice versa

BURTON I don't believe that Dr Sarnoff really asked me a question I was very interested to hear about this critical closing pressure being 6 cm of water, because my point is that if this smooth muscle, which is capable of contorting and constricting the small vessels normally, does go into action, I am quite sure that the critical closing pressure will rise considerably. If it does rise considerably, then I would think that this would make a lot of the small vessels close down completely

As to the other remarks, about the interpretation of resistance, I would agree completely. In my thinking, it made an enormous difference when we separated clearly the 'driving pressure' which governs the normal flow, given a certain resistance, and 'transmural pressure,' which governs the size of the vessels I would recommend to all of you and to your thinking, this clear separation of the two pressures involved in hemodynamics

FORSTER. One of the major problems that has been worrying me for sometime is the question of distensibility of the capillaries and I wonder if Dr Burton had anything to offer in that line or what does he think of the gnarly vessels?

BURTON Well, we were not able to get casts of the capillaries The cast method gives us no information about the capillaries The only capillary distensibility we have measured was on the capillaries of the frog, and the astonishing thing is that here one can detect no increase in diameter, even with a rise of 100 mm.Hg in the capillary pressure The tiniest resistance to stretch, in such a small cylinder, would resist a very great pressure indeed, because of the law of Laplace

One of the cutest ways of demonstrating the nondistensibility of the peripheral capillaries is to get some small bubbles in them The pressure inside a bubble is considerably more than the pressure in the blood on each side of it, due to the surface tension. When one has a bubble one cannot see that the capillary wall is any more distended at the bubble than on either side of it

I think that the capillaries are remarkably resistant to pressure distension. At the same time, I recognize that, physiologically, capillaries do dilate enormously, under chemical stimuli rather than under increased pressure, and I do not understand how this happens.

# Instantaneous Pulmonary Capillary Blood Flow

*By* Arthur B. DuBois

Nitrous oxide is so soluble in blood or water that it is immediately picked up by blood entering the capillary bed of the lungs. If the subject is in a closed chamber and takes a breath of nitrous oxide, the pressure then falls at a rate which indicates the rate of absorption of the gas by the blood and consequently the rate of pulmonary capillary blood flow The instantaneous rate of pulmonary capillary blood flow can be calculated provided we know the concentration of the gas and the solubility in blood ($\dot{Q} = (\dot{V}_{N_2O} \cdot S_{N_2O} \cdot FA_{N_2O})$.

This principle has been tested using a very simple system[1] Heparinized rabbit lungs were removed and suspended in a bell jar The lungs were inflated with air containing 5 per cent $CO_2$ but no nitrous oxide Ringer's solution, through which 5 per cent $CO_2$ had been bubbled, was pushed through the vascular bed by means of a syringe, also in the bell jar space No change in pressure occurred within the bell jar (fig 1, top) until late in the record because there was no nitrous oxide in the lungs, and exchange of other gases was slight However if the lungs were then ventilated with nitrous oxide, the gas partial pressure equilibrated within less than a second and the pressure in the plethysmograph became steady (fig 1, bottom) There was then no trend in pressure until fluid began to flow into the capillary bed, where gas absorption took place The pressure proceeded to fall at a rate indicating the rate of perfusion of the capillary bed The position of the syringe barrel is recorded at the bottom of the record, and injection began at time zero About 13 ml of Ringer's solution were injected in about 10 seconds The plethysmographic pressure fell indicating absorption of about 4.5 ml of gas Pressure in the blood vessel (this was perfusion of the pulmonary artery) rose to about 10 cm $H_2O$ during injection Note that gas absorption was negligible until about 1 3 ml of fluid had been injected, a volume required to fill up the pulmonary arterial tree prior to full capillary flow The pressure change by that time was 7 cm $H_2O$ 1 3 ml divided by 7 cm $H_2O$ yielded a compliance of the pulmonary arterial vascular tree of 0 19 ml /cm $H_2O$, which represented the elastic capacity of the vascular bed proximal to the point of gas exchange during increasing pressure Compliance of the venous tree, measured by retrograde perfusion in this lung, was about two to three times the compliance of the arterial tree Together, the compliance of the arterial and venous tree

*This work was done during the tenure of an Established Investigatorship of the American Heart Association.*

*This work is based on the combined efforts of Dr Julius H Comroe, Jr, Dr Grant de J. Lee, Dr Robert Marshall, Dr. Robert E Forster, II, Dr Joseph Engelberg, and Dr Philip Kimmel, all of whom have participated in various aspects of the work*

*This investigation was supported, in part, under a contract between the Army Chemical Center and the Graduate School of Medicine, University of Pennsylvania*




FIG 1 —Perfusion of pulmonary artery of isolated rabbit lungs in a closed space Upper record, lungs inflated with 5% $CO_2$, balance air Lower record, lungs containing approximately 80% $N_2O$ Plethysmographic pressure, pulmonary arterial pressure, and volume of infusing syringe run at 75 ml of Krebs Ringer's solution per minute [1]

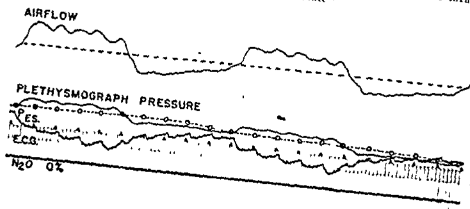



FIG 2 —Subject seated in a body plethysmograph and rebreathing warm, humidified air in a bag Open circles are corrections for fluctuations in plethysmographic pressure due to resistance to airflow Slight trends of pressure are due to respiratory exchange ratio This is the control record for figure 3

accounted for 85 per cent or more of the compliance of the whole vascular bed measured by clamping it off and raising the pressure by injecting small volumes of fluid Thus indicated that the arterial and venous regions of the pulmonary vascular bed were quite capable of distension, whereas the capillary bed did not accommodate much extra fluid under pressure [2]

Now let us turn to some measurements made on man The subject was seated in a body plethysmograph If he rebreathed warm humidified air in a bag, there was only a slight trend in plethysmograph pressure because very little gas exchange took place (fig 2) We have made corrections for the small

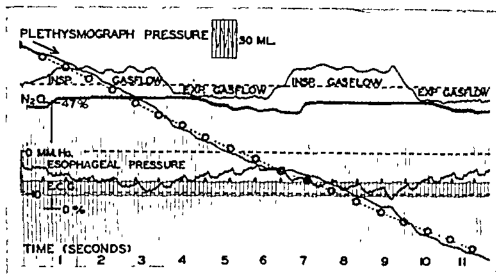



FIG 3.—Same recording as figure 2 except that the bag was filled with $N_2O$ whose concentration was recorded by an infra red gas analyzer Absorption of $N_2O$, shown by open circles which are corrected for resistance to airflow, was at the same rate during inspiration and expiration [3]

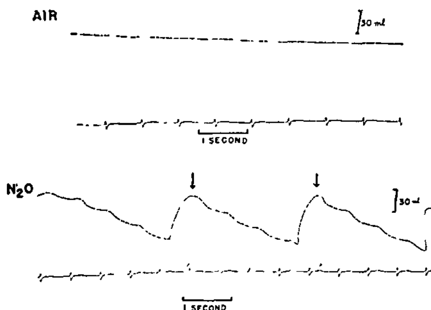



FIG 4—Plethysmographic pressure change and ECG while subject held his breath on air (upper record) or on nitrous oxide (lower record) The uptake of the latter is pulsatile with the heart rate Plethysmograph vented to atmosphere at arrows [4]

swings in volume which were attributable to resistance to airflow (open circles) When we had the subject rebreathe in a bag containing 80 per cent $N_2O$, 20 per cent $O_2$, we recorded a fall in plethysmograph pressure owing to absorption of $N_2O$ by blood flowing through the pulmonary capillary bed

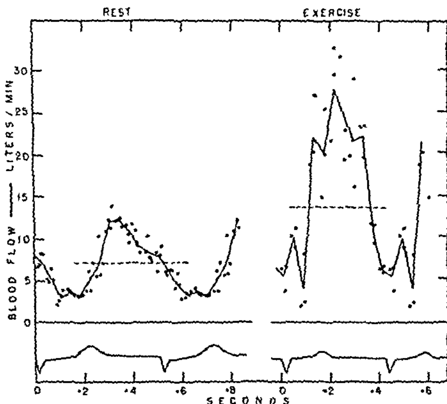



FIG 5.—Instantaneous pulmonary capillary blood flow curve replotted by measuring a record such as that in figure 4 at 0.04 second intervals, subtracting the control record from the $N_2O$ record, and superimposing four heart cycles timed from the R wave. At rest, and after exercise [4]

Again, the same correction for airway resistance was made (fig 3). Gas absorption proceeded during both inspiration and expiration, indicating that pulmonary capillary blood flow was quite even (inspiratory-expiratory blood flow averaged 1 per cent difference, SD 7.7 per cent) throughout the normal respiratory cycle [3]

The corrected points in figures 2 and 3 were all measured at the same phase of the cardiac cycle. However when the subjects were asked to stop breathing for a few seconds, to abolish artifacts attributable to alveolar pressure swings, we could examine in more detail the gas absorption and pulmonary capillary blood flow changes which occurred throughout all phases of the cardiac cycle (fig 4). The top record was made while the subject was holding his breath while breathing air, whereas the bottom record was the same subject holding his breath while breathing nitrous oxide. The box was vented to atmospheric pressure at the arrows. The plethysmographic pressure fell not in a smooth line, but in intermittent fashion over the ten second period of breath holding. Upon comparison with the electrocardiographic record underneath, one can see that gas absorption was most rapid during systole, and almost negligible at the end of diastole

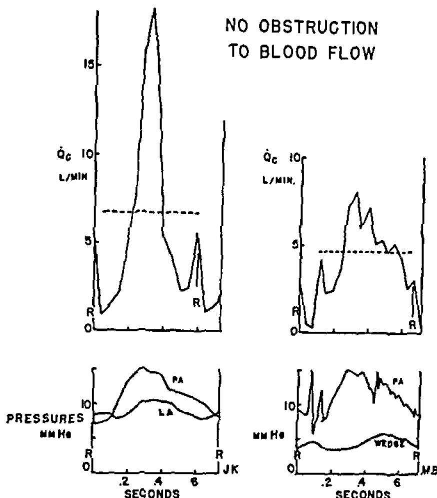



FIG 6 —Instantaneous pulmonary capillary blood flow and pulmonary vascular pressures obtained by catheterization of the same subjects on different days Two subjects who did not have pulmonary vascular disease Note the close relationship between the pressure gradient and the blood flow Diastolic and presystolic notches are often visible in both waves [5]

Replotting these curves as instantaneous pulmonary capillary blood flow, we obtained a very pulsatile wave of flow (fig 5) either at rest, or after moderate exercise [4] The fluctuating flow may be compared to the fluctuating pressure gradient between the pulmonary artery and left atrium measured at catheterization on a different day but in the same patient [5] Two such comparisons are shown in figure 6

So far, we have considered the experimental results obtained using the plethysmographic nitrous oxide method several ways Now let us speculate about the implications of these results and about what we hope to learn by further use of the method

*Work and Energy of Blood Flow in the Pulmonary Arterial Tree*

During systole, blood is accelerated in the right ventricle and pulmonary artery by contraction of the right ventricle The blood gains kinetic energy,

or energy of motion. As blood distends the arterial tree the latter acquires potential energy (elastic and hydrostatic). At the same time, energy is partly dissipated by resistance to systolic flow in the small vessels During diastole, the potential energy in the arterial tree is partly lost in hysteresis, and the remainder is dissipated during elastic recoil as blood flows through the resistance of the small vessels By the end of diastole, the pressures in the vascular bed are almost equilibrated, and capillary flow practically ceases.

*Hemodynamic Factors which Oppose Forward Flow of Blood in the Pulmonary Arterial Tree*

The acceleration of pulmonary capillary blood flow (Qc) during systole was measured from five normal resting curves in reference 4 The values for acceleration were 1.3, 1 2, 1 6,1 6 and 2 8, averaging 1 7 L /sec /sec Acceleration of blood in the main pulmonary artery cannot be much less than this for two reasons First, because the right ventricle empties itself so quickly, and second, because flow appears in the capillaries so soon If the cross sectional area of the pulmonary artery were 4 cm $^2$, the volume of blood accelerated were 100 ml , and the acceleration were 1.7 L /sec /sec , then applying Newton's Law, force equals mass times acceleration, the pressure in the right ventricle to produce this acceleration would be 8 mm.Hg

The elastic recoil of the pulmonary arterial tree during diastole has been calculated assuming that the volume of blood which leaves the pulmonary arterial tree during diastole, ΔQ, is the same as the volume of blood which enters the capillary bed during diastole, and that it can be measured on the capillary flow curves as the area under the curve during the diastolic interval of time (O to t) $\Delta Q = \int_0^t \dot{Q}\, dt$ In a normal vascular bed, this volume was 20 ml , about one-quarter of the stroke volume During diastole, the pulmonary arterial pressure change was $\Delta P = 3\ 5$ mm Hg, in the same subject, but catheterized on a different day. Compliance of the pulmonary artery was $C = \Delta Q/\Delta, P = 20/3\ 5$ or 5 7 ml /mm Hg.

The resistance to blood flow in the pulmonary vascular bed may be calculated as the ratio of mean pressure gradient to mean blood flow Dexter et al obtained a mean resistance of 67 (range 47 to 87) dynes sec cm$^{-5}$.[6] Our impression is that taking the ratio of mean pressure gradient to mean flow is probably reasonably correct for expressing the resistance of the small vessels (arterioles, capillaries plus venules) because the pressure wave and flow wave are so similar in form

The lag of the flow wave with respect to the pressure wave appears to be about 0 1 (0 0 to 0 2) sec , but will not be known more precisely until simultaneous measurements have been made of pressure and flow. A lag of this degree could be explained on the basis of pulse wave velocity

The opening pressure of the small vessels has been described by Dr Burton Since the flow and pressure vary so strikingly during a single heart beat, we should be able to see during systole whether there is a marked rise in pressure prior to the onset of capillary flow This effect could be studied in records such as those obtained from the isolated lung In the human records, a pressure prior to opening might go unnoticed because of the rapidity of ejection of the

right ventricle and possibly because of the time necessary for the transmission of the pulse wave.

### *Alterations in Pulmonary Vascular Disease*

Although we are unable to say how much of the resistance to blood flow is precapillary, intracapillary and postcapillary, there is a possibility of distinguishing the capillary curves found in the presence of a marked increase of precapillary resistance from those found when there is a marked increase in postcapillary resistance By comparison of the relationship between the pulse pressure curves and instantaneous capillary flow curves it was apparent that increased precapillary resistance may have attenuated the capillary flow curve (diminished its peak amplitude and delayed the peak flow with respect to peak pressure) through a Windkessel effect However, increased postcapillary resistance did not appear to attenuate the pulse flow curve in the capillaries An increase in resistance would raise the pulmonary arterial pressure during flow, and this would in turn distend the pulmonary arterial tree, resulting in decreased compliance of it either by approach toward an elastic limit or by a change in the walls of the vessels In a case of pulmonary hypertension, the diastolic compliance was calculated to be 21 5/11 0 or 2 0 ml /mm Hg, which is considerably less than that of the normal lung

A horizontal plastic plethysmograph designed to fit on a fluoroscope table has been constructed for simultaneous measurement of instantaneous pulmonary capillary blood flow and intravascular pressures during cardiac catheterization * With this, it should be possible to make simultaneous measurements of pressure and flow in individual patients This should allow the measurement of compliance of the pulmonary arterial tree, location of resistance to flow in pulmonary hypertension, beat by beat variations of right ventricular stroke volume, and variations of vascular compliance and resistance in different phases of the heart cycle and during heart beats of different stroke volume or duration †

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* Made for us by Air Shields, Inc, Hatboro, Pa

† Although the method is apparently applicable to research, we do not at present regard it in any sense as a routine clinical method for cardiac output owing to the limitations discussed in references 3 and 4

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## DISCUSSION

SARNOFF This ingenious technique of Dr DuBois is a much needed approach to work in the field

Dr DuBois, the explanation you gave concerning the delay in the plethysmographic pressure change after the onset of the infusion of the pulmonary vascular bed is certainly a plausible one You apparently feel this delay is due to the filling of the vessels when the pump is started and that this is prior to the *onset* of actual capillary flow I wonder if we wouldn't feel a bit more convinced about this if you gave us information concerning whether or not this delay in the plethysmographic response is mitigated or abbreviated when the vessels are predistended That is to say, if you filled them first and then initiated the system so that capillary flow started immediately, would your plethysmographic tracings still not show an immediate drop?

DUBOIS We have not investigated all combinations of pressure in either the arterial side or the venous side, and we have not investigated all combinations of lung inflation as Dr Burton and you, and Dr Berglund have approached it

SARNOFF Is there any indication from your data, Dr DuBois, that there is a pulmonary capillary flow rate within reach which, if exceeded, will begin to interfere with saturation of the blood in its traverse of the capillary circuit?

DUBOIS It is conceivable that the pulse during systole might get through so fast that the blood doesn't have time to saturate with oxygen, and diastole would not make up for this in a person with impaired diffusion and increased cardiac output Nitrous oxide is much more diffusible than carbon monoxide or oxygen It is more like carbon dioxide It does go into solution very quickly (in about one-twentieth of a second)

DEXTER I would like to say, first of all, that this is a really remarkable method, as I am sure you all appreciate Methods of measuring blood flow instantaneously have been sought for years Flow meters have been used in animals, but in man Dr DuBois' technique is the only method available Furthermore, it pinpoints the measurement to the all-important capillary bed of the lung

By simultaneous measurements of pressure and flow, his work also emphasizes the lack of linearity between pressure and flow, as Dr Burton pointed out, and this raises the question of how great the change in *calculated* resistance must be before there is a change of *actual* resistance His ability to calculate the impedance is an important contribution

From what Dr DuBois says, I gather that there is no evidence as yet that

blood actually comes to a standstill or runs backwards in the capillaries in mitral insufficiency

I should like to ask Dr. DuBois one question The body plethysmographic method measures the total pulmonary capillary flow The Fick method measures the pulmonary arterial flow. The plethysmographic minus the Fick should theoretically measure the bronchial collateral circulation as well as blood shunted around the pulmonary capillary bed I wonder if this would be a practicable measurement to make.

DuBois In a few people with vascular shunts we found the method unsatisfactory because of recirculation. Our method requires about a ten second period of breath-holding. In the presence of recirculation, instead of getting a steady rate of uptake you can rely on, you get a curved line It is true that you might be able to discover some things about them, but I don't think it is going to prove a very good method for studying pulmonary vascular shunts. This is a good way of studying pulsatile pulmonary capillary flow curves but not a good way of studying shunts Fortunately there are other ways of studying them.

# The Pulmonary Capillary Bed: Volume, Area and Diffusing Characteristics

*By* Robert E. Forster

This presentation consists of a brief outline of methods we have developed for the measurement of the diffusing capacity of the pulmonary capillary membrane ($D_M$), the pulmonary capillary blood volume ($V_c$), the volume of the parenchymal tissue of the lung ($V_T$), and the pulmonary capillary blood flow ($Q_c$), plus some results we have obtained from the application of these methods to humans. This work has extended over about the last 8 years, and my associates have contributed a majority of the effort, in ideas as well as labor. Some of the data I shall mention have not yet been published in full. Because our methods of observation are based on gas exchange processes in the lung, I will define the pulmonary capillaries as those vessels of the lung across whose walls significant exchange of gases takes place between the alveolar air and the blood.

First, I will outline the method which Professor Roughton and I have developed for the measurement of $V_c$ and $D_M$.[1,2] $V_c$, it should be pointed out, is the capillary blood volume, something in the order of 90 ml. in resting normal man, and not the total pulmonary blood volume, in the order of 1 liter (3). $D_M$, the diffusing capacity of the pulmonary membrane, is the rate at which a specified gas, and I will be talking about CO, diffuses across the alveolar membrane, in ml./min./mm Hg of CO tension difference. It does not include the movement of CO within the blood. $D_M$ is theoretically directly proportional to (a) the total surface area of the pulmonary capillary bed, (b) the specific diffusivity of the tissues making up the pulmonary membrane, (c) the solubility of CO in the membrane ($\alpha_M$), and (d) inversely proportional to the thickness of the membrane. Assuming for the lack of contrary information, that the specific diffusivity and solubility do not vary over a wide range, $D_M$ becomes a composite index of changes in the surface area of the pulmonary capillary bed and the thickness of the membrane. $D_M$ is to be distinguished from the pulmonary diffusing capacity, $D_L$, which includes both the process of diffusion across the pulmonary membrane and, in addition, the combined diffusion-reaction processes within the blood. The pertinent pressure gradient in the case of $D_L$ is that from the alveolar gas to the intracorpuscular Hb molecule, and since the CO tension in the vicinity of the Hb molecule is zero (or is corrected to zero[1]), equals the alveolar CO tension. $D_L$ is determined by a modification of the breath holding technique described by Drs. Fowler, Bates, Van Lingen and myself several years ago.[1] The subject inhales a single measured volume of a gas mixture containing about 0.4 per cent CO, and 10 per cent helium, the remainder consisting of various proportions of

*This work was supported in part by a grant from the Life Insurance Medical Research Fund.*

blood actually comes to a standstill or runs backwards in the capillaries in mitral insufficiency

I should like to ask Dr DuBois one question. The body plethysmographic method measures the total pulmonary capillary flow. The Fick method measures the pulmonary arterial flow The plethysmographic minus the Fick should theoretically measure the bronchial collateral circulation as well as blood shunted around the pulmonary capillary bed. I wonder if this would be a practicable measurement to make

DuBois. In a few people with vascular shunts we found the method unsatisfactory because of recirculation Our method requires about a ten second period of breath-holding. In the presence of recirculation, instead of getting a steady rate of uptake you can rely on, you get a curved line It is true that you might be able to discover some things about them, but I don't think it is going to prove a very good method for studying pulmonary vascular shunts This is a good way of studying pulsatile pulmonary capillary flow curves but not a good way of studying shunts Fortunately there are other ways of studying them

and 32.1 ml $\pm$ 2 3 ml /min./mm Hg for $D_L$ at an alveolar $P_{O_2}$ of 120 mm Hg At this last $P_{O_2}$ the intracapillary resistance to CO uptake ($\theta V_c$) is 47 per cent of the total. Of course, it must be borne in mind that very large errors in $D_M$ can result from relatively minor errors in the estimates of $D_L$, a fact inherent in the calculation This makes $D_M$ a far less reliable measurement than $V_c$

I will now go on to outline the method Dr. Cander and I have developed for the measurement of the pulmonary tissue volume ($V_T$) and the pulmonary capillary blood flow ($Q_c$) [7] The experimental technique is similar to that I have already described for the estimation of $D_L$, except that the subject inspires a gas mixture approximately as follows 0 5 per cent acetylene, 10 per cent helium, and the remainder $N_2$ and $O_2$ If expired alveolar samples are collected after a period of breath holding, ranging from about 2 to 50 seconds, and if these samples are analyzed for acetylene and helium, and the acetylene concentration expressed as a fraction of the value predicted from the dilution of helium in the residual gas, results similar to those in figure 1 are found This represents 8 separate experimental measurements The immediate drop in alveolar acetylene concentration results from the rapid solution of this gas in the finer parenchymal tissues of the lung, the septa and the pulmonary membrane The volume of these tissues which are exposed to the alveolar gas we have called pulmonary tissue volume and designate as $V_T$ If we know the alveolar gas volume ($V_A$), and the solubility of acetylene in the lung parenchyma ($\alpha_T$), we can calculate $V_T$ from the intercept of the acetylene disappearance curve on the ordinate Dr Cander has determined the value of $\alpha_T$ at 37°C for the parenchymal tissue of cadaver lungs which were dissected free of the larger airways and blood vessels, as 0 768 ml /ml /atmosphere $V_T$ in the subject in figure 1 was 630 ml The average value of $V_T$ in 5 normal subjects was 570 ml, corresponding very well with an average value of 580 ml for the volume of the cadaver lungs minus pulmonary capillary blood volume

Assuming there is no acetylene in the pulmonary arterial blood, Qc is theoretically proportional to the slope of the disappearance curve in figure 1, precisely, the slope equals $-\dot{Q}_c\alpha_B(V_A + \alpha_T V_T)$ $\alpha_B$ and $\alpha_T$ have been obtained from in vitro measurements, $V_T$ can be calculated from the intercept in figure 1 as discussed above, and $V_A$ equals the inspired volume plus residual volume Therefore, we know enough to calculate $\dot{Q}_c$ from the slope in figure 1; its value is 6 9 L /min I do not want to enter into the controversy concerning the accuracy of the inert gas methods for cardiac output as compared with the direct Fick [9,10,11] but I should mention several points in this regard The first is that recirculation can be detected as an upward curvature of the acetylene disappearance curve In figure 1, the curve is straight until about 20 seconds of breath holding, well within the time necessary to make the needed measurements, which can be completed in 10 seconds or less The second point concerns the magnitude of the results The average resting pulmonary blood flow in 5 normal resting men was 3 14 L /min /$M^2$ (Cander and Forster, to be published), which is consonant with the average value of 3 12 L /$M^2$ reported by Cournand et al [12] for basal subjects using the direct

$O_2$ and $N_2$ Breath is held for about 10 seconds, and then exhaled Approximately the first liter, or an approximate amount, is discarded as being contaminated with dead space gas, and a portion of the remainder collected and considered *alveolar* gas Helium is practically insoluble in blood and tissue, so its concentration in the alveolar sample, as compared with that in the inspired gas, represents the dilution of the inspired gas by the gas residual in the lung The inspired CO must have been diluted in exactly the same ratio, so the helium dilution can be used to calculate the CO concentration that would have been present in the alveolar sample, if some CO had not been absorbed by the blood This calculation therefore gives the alveolar CO concentration at the start of the period of breath-holding, the actual CO concentration in the alveolar sample is that at the end of this period Since we know the initial and final alveolar CO concentrations, the total alveolar gas volume ($V_A$) and the time, we can calculate the rate of CO passage into the blood, the average alveolar $P_{co}$ during the breath-holding period,* and therefore, $D_L$, which equals the rate of CO uptake per mean alveolar $P_{co}$ $D_L$ is greater in individuals with larger body surface area, increases in exercise, is decreased in diseases of the pulmonary capillary, such as alveolar-capillary block, and decreases in an individual when the alveolar $P_{O_2}$ is raised [1,4,5] This decrease in $D_L$ with an increase in alveolar $P_{O_2}$ results because $O_2$ competes with CO for the reduced Hb in the red cell, slowing down the rate of formation of COHb in the blood to such an extent that CO diffusing across the pulmonary membrane into the plasma piles up, raising the plasma dissolved CO tension, which interferes with the further movement of CO out of the alveolar air At an alveolar $P_{O_2}$ of 600 mm Hg, $D_L$ is about one-half that breathing air (alveolar $P_{O_2}$ 100 mm Hg), and plasma $P_{co}$ is about 75 per cent of alveolar $P_{co}$, the rate limiting process is that of the formation of COHb within the red cells The rate of COHb formation in turn depends upon the velocity of formation of intracellular COHb per ml blood,† which can be obtained in vitro,[6] multiplied by the total volume of blood in the pulmonary capillary bed ($V_c$) On the other hand, at an alveolar $P_{O_2}$ of 100 mm Hg, $D_L$ depends about equally on $D_M$ and the total rate of COHb formation in the capillary bed Using measurements of $D_L$ at several alveolar $O_2$ tensions, we can calculate $D_M$ and $V_c$ alone ‡

The most recent and extensive data on $V_c$ and $D_M$ we have at the moment are those of McNeill, Rankin and Forster (Clinical Science, in press) on 8 normal resting male subjects with an average surface area of 2 square meters giving values of 97 3 ± 16 0 ml for $V_c$, 63 5 ± 12 4 ml /min /mm Hg for $D_M$,

* This is not a simple average of the initial and final concentrations Actually, $D_L = V_A /$ (time of breath holding × [barometric pressure − 47 mm Hg]) × natural logarithm (initial alveolar CO concentration/final alveolar CO concentration)

† This velocity constant, usually called "$\theta$", is in units of ml CO/min mm Hg $P_{co}$/ml whole blood Its value at a $P_{O_2}$ of 120 mm Hg is 0 83, and at 600 mm Hg, is 0 24 [6]

‡ The relation between the pertinent variables is most succinctly expressed in the equation, $1/D_L = 1/D_M + 1/\theta V_c$ $D_L$, $D_M$ and $\theta V_c$ are analogous to electrical conductances and their reciprocals to electrical resistances The equation thus states that the total resistance to the uptake of CO equals the resistance to diffusion across the pulmonary membrane proper plus the resistance to the entrance of CO into the red cells

the gas dissolved in the lung tissue, in addition to that lost from the alveolar air. Obviously this method for estimating pulmonary blood flow can only be influenced by those parts of the lung which contribute significantly to the expired alveolar sample. Also, since the disappearance curve has two unknowns, $\dot{Q}_c$ and $V_T$, in order to solve the relationships it is necessary to obtain two points,* one as early as possible which is influenced mainly by $V_T$, and a later point, such as around 10 seconds, which depends mainly on $\dot{Q}_c$ Alternately, a value for $V_T$, which is apparently stable, can be assumed from later measurements

Drs Johnson, Spicer and Bishop have gone on to combine the method for $D_M$ and $V_c$ with that for $Q_c$ and $V_T$ By having the subject make an inspiration of a gas mixture containing approximately 0 4 per cent CO, 0 5 per cent acetylene, 10 per cent helium and the remainder $N_2$ and $O_2$, we can obtain simultaneous measurements of $D_L$ and $Q_c$

I will now discuss some results, which we have obtained with these methods, relating to the mechanism of changes in the pulmonary capillary bed

Exercise has been known to increase $D_L$ since the first work of Krogh [14] Figure 2 is a graph of $D_L$ at a normal alveolar $P_{O_2}$, about 120 mm Hg in one normal subject at varying states of exertion The data are from the work of Drs Johnson, Spicer, Bishop and myself Valsalva done during the period of breath-holding lowers pulmonary blood flow below resting values, while several minutes of exercise raises it $D_L$ is approximately a linear function of $Q_c$, with intercept on the ordinate greater than zero This suggests that there would be stagnant blood in the capillaries to absorb CO even if the total blood flow were zero The data in this and the subsequent figures were similar for all subjects studied

Figure 3 and figure 4 show the values of $V_c$ and $D_M$ calculated from the values of $D_L$ in figure 2 plus similar data at higher alveolar $O_2$ tensions Both $V_c$ and $D_M$ are also linear functions of $Q_c$ although the data for the latter are the more variable $V_T$, the corresponding measurements of which are not shown, had an average value for Subject WSS of 526 ml, and ranged from 298 to 712 ml with no correlation with $Q_c$ This datum is extremely sensitive to slight changes in the intercept of the acetylene disappearance curve (fig 1) The average time a red cell remains in the pulmonary capillary bed equals $V_c/\dot{Q}_c$ and for the data in figure 3 ranges from 1 2 seconds at $Q_c = 4$ L/min to 0 5 second, when $Q_c = 15$ L/min

These results suggest that any change in cardiac output changes both the volume of blood in the pulmonary capillary bed and the effective surface area of the bed There appears to be no plateau, at least up to a cardiac output of 14 L/min If this is simply a passive opening of the vessels, then a sudden change in cardiac output should produce an equally sudden change in the capillary bed In figure 5 are plotted simultaneous values of $D_L$ and $Q_c$ at different times during a period of exercise and subsequent return to the resting state $V_T$ was assumed constant throughout The procedure was repeated

* To obtain both on a single breath holding experiment, $V_T$ is assumed from other data

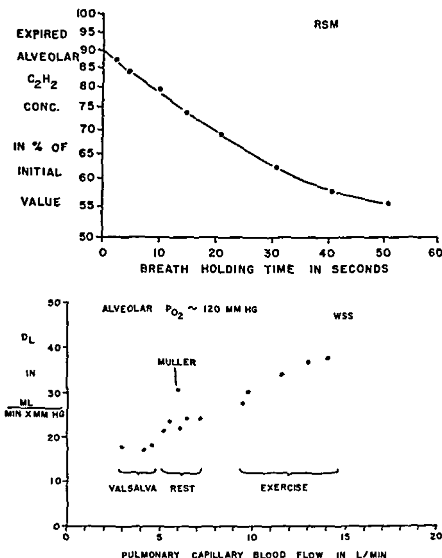



FIG. 1 —(*top*) A graph of expired alveolar $C_2H_2$ concentration plotted against the duration of breath holding The $C_2H_2$ concentration on the ordinate is expressed as a percentage of the value calculated from the dilution of the inspired helium in the residual air In other words, 100 (Expired alveolar $[C_2H_2]$ $\times$ Inspired [helium])/(inspired $[C_2H_2]$ $\times$ expired alveolar [helium]) The ordinate is a logarithmic scale, not linear.

FIG 2 —(*bottom*) A graph of diffusing capacity of the lung ($D_L$) plotted against pulmonary capillary blood flow ($Q_c$) at rest, during exercise on a treadmill, and during Valsalva and Muller maneuvers in Subject W S S Alveolar $P_{O_2}$ was approximately 120 mm Hg

Fick technique In addition, the values of pulmonary blood flow during exercise (around 1 2 L/min/$M^2$) are within 10 per cent of those reported by Donald et al [13] for subjects exercising supine using the direct Fick technique Previous failures to allow for the tissue volume must have led to an underestimate of the pulmonary blood flow by the inert gas methods in the order of 10 per cent, since a change in alveolar concentration indicates a change in

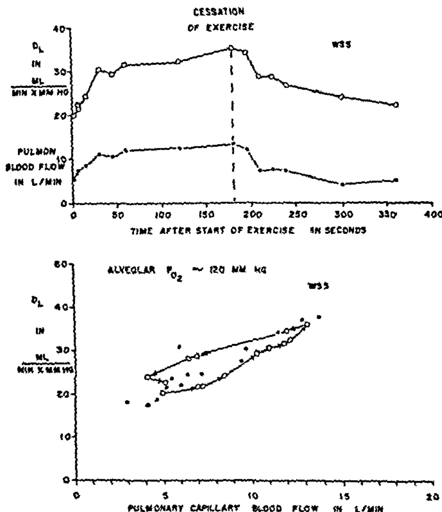
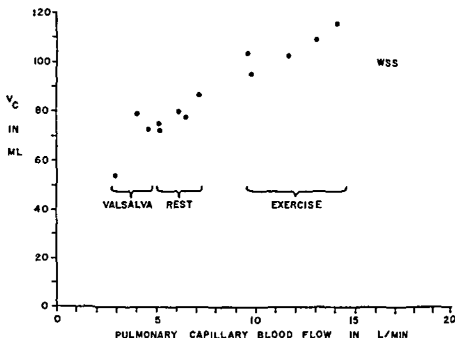



FIG 5.—(*top*) Simultaneous measurements of pulmonary diffusing capacity ($D_L$) and pulmonary capillary blood flow ($Q_c$) in Subject W S S at different times during and after 3 minutes of exercise on a treadmill ($O_2$ consumption about 1600 ml/min) The exercise was repeated to obtain each point

FIG 6.—(*bottom*) A graph of pulmonary diffusing capacity ($D_L$) against pulmonary capillary blood flow ($Q_c$) in Subject W S S for the transient conditions *during and after* 3 minutes of exercise (fig 5) (*open circles*) The arrows indicate the chronological order of the data, the arrow heads point to the later measurements The "steady state" values of $D_L$ shown in figure 2 are included here as solid dots for comparison.

to obtain each point. The rapidity of the changes in both $Q_c$ and $D_L$ is striking, as is the marked similarity in the two curves A reasonably steady state was achieved in about one minute, as has been reported by Donald et al [13] I have plotted these values of $D_L$ against $Q_c$ in figure 6 as open circles, and



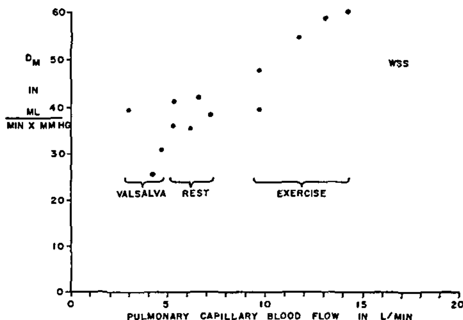




FIG 3.—(*top*) A graph of pulmonary capillary blood volume ($V_c$) plotted against pulmonary capillary blood flow ($Q_c$) at different states of exertion in Subject W.S S

FIG 4 —(*bottom*) A graph of diffusing capacity of the pulmonary membrane ($D_M$) plotted against pulmonary capillary blood flow ($Q_c$) at different states of exertion in Subject W S S

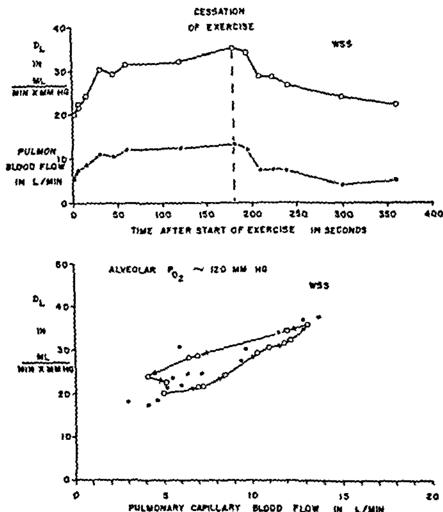



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have included the *steady state* values shown earlier (fig. 2) as solid dots to bring out the relationship between the transient and steady state values There is certainly a tendency for the blood flow to increase more rapidly than $D_L$ at the start of exercise, and the reverse at the cessation of exercise. This change is significant, at least at certain parts of the cycle, but it is difficult to say whether this is due to a mechanical lag, or represents the delay in some control mechanism, such as a reflex In this particular, it would be enlightening to know what happens to the pulmonary artery pressure during this transient phase, although it is dangerous to assume the capillary bed contributes a major part of the pulmonary vascular resistance

What are the changes in the dimensions of the capillary bed with change in cardiac output? Do the individual capillaries expand, or do capillaries previously shut, open up? If the latter mechanism is the more important one. $D_M$ and $V_c$ should increase proportionally, since the process consists essentially of adding new capillaries to the bed, assumedly of the same size On the other hand, if capillaries already patent are distended during the increased blood flow, $V_c$ would probably increase proportionally more than $D_M$, as the volume increases more rapidly than the surface area when the radius of a cylinder increases The values of $D_M$ for all 4 subjects studied are plotted against $V_c$ in figure 7 The regression line of $D_M$ as a function of $V_c$, excluding the one aberrant point, is also given If $D_M$ varied in the same proportion as $V_c$, this line should pass through the origin, which it does not However, a similar line for several of the individual subjects would pass close to the origin Unfortunately, it is not possible to distinguish between these two different mechanisms of increasing the capillary bed, although further studies

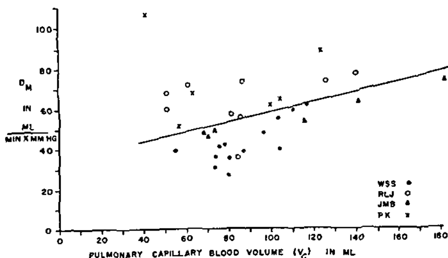



FIG 7 —A graph of the diffusing capacity of the pulmonary membrane ($D_M$) against pulmonary capillary blood volume ($V_c$) in 4 normal subjects at different degrees of exertion (Johnson, Spicer, Bishop and Forster, to be published) The datum of PK at $Q_c = 40$ ml and $D_M = 106$ ml per min per mm Hg was omitted from the regression line The regression equation is $D_M = 34.0 + 0.22\ V_c$

might bring out a difference If the pulmonary hematocrit altered with changes in $Q_c$, the relationship of $D_M$ and $V_c$ would change[5] An increase in hematocrit would produce an apparent increase in $V_c$, even if the actual blood volume were constant

Several miscellaneous findings suggest that the relationship between $D_M$, $V_c$ and $Q_c$ may not be just a simple passive opening up of the capillary bed with increased flow Drs Johnson, Kimmel and Stein (to be published) studied 10 patients with thyrotoxicosis and found $D_L$ within normal limits (certainly not increased) in spite of measured increases in $Q_c$ Dr D V. Bates and associates (personal communication) have made similar observations during moderate exercise using a steady state method of measuring $D_L$. In our patients, there was no significant fall in $D_L$ with treatment, although $Q_c$ as measured in the body plethysmograph using $N_2O$ fell in all 5 of the patients in whom it was estimated This suggests that chronic increases in $\dot{Q}_c$ may not necessarily be accompanied by increases in the dimensions of the pulmonary capillary bed, or possibly that some pathological process associated with the disease compensates for increase resulting from greater $\dot{Q}_c$. In reference to this last possibility, measurements of $D_M$ and $V_c$ in 2 of patients before and after treatment, showed no change

Another slightly disconcerting finding is that normal seated subjects showed no change in $D_M$ or $V_c$, when a pressure suit fitted about the lower half of their body was suddenly inflated for 20 to 30 seconds[15] Previous studies with venous catheterization had demonstrated that under the conditions used this procedure raised pressures throughout the pulmonary vascular circuit about 20 mm Hg, and although simultaneous vascular pressure measurements were not taken at the time of experiments, it is reasonable to assume that the pressure across the pulmonary capillary walls rose considerably, apparently without increasing the size of the capillary bed Gas was trapped in the lungs during the procedure, which may have distorted the calculated values of $D_L$, but the results certainly suggest that the capillaries are not simply distended by a sudden increase in the pressure across their walls Stimulated by these findings, Miss Edith Rosenberg and I are investigating the effect of transmural pressure on the capillary bed in isolated perfused cat lungs

I have said nothing about the surface area of the capillaries or the thickness of the pulmonary membrane There are at present no satisfactory methods for independently measuring either the area, effective thickness of the wall or diffusivity of the tissue making up the pulmonary membrane Dr Radford has devised a very ingenious method[16] for estimating the total surface area of the lung, but this is not necessarily the same as that of the capillary bed

In summary, we have developed a breath-holding technique for the estimation of the diffusing capacity of the pulmonary membrane, the volume of blood in the pulmonary capillaries, the blood flow through the pulmonary capillaries, and the pulmonary tissue volume I have shown you some of the results that my associates and I have obtained with this method, results indicating the extremely close relationship between blood flow through the pulmo-

nary capillary bed and its dimensions I don't think we can draw any startling conclusions about the mechanism of control of the bed at this time, though I look with anticipation to the future.

Finally, I would like to pay a tribute to Dr. J H. Comroe, Jr. and Dr. Seymour S Kety, who, local rumor hath it, laid the plans for all this work in a mere 48 hours in *1950*, and it has taken my other colleagues and myself 8 years to get this far

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## Discussion

Riley · I am impressed by Dr. Forster's magnificent work which leads him to a perfectly astounding combination of techniques for getting at some of the most complicated aspects of gas exchange

I am certainly not able to comment on the validity of the technique de-

scribed. Like all techniques, they are approaches to what is not necessarily a perfect answer. My only comment in that regard is to suggest that the decimal place be left off on the results that are obtained because that degree of accuracy is as yet unattainable by any methods in this field

There is no doubt about the general significance of the work which Dr Forster and various collaborators (particularly Dr Roughton on the theoretical side) have done It has added a whole new dimension to our thinking about the movement of gas from the alveoli to the red blood cells

Most of us have been aware that various stages were involved and could name them if we were publishing a paper, but thought that for working purposes, the dominant resistance to the movement of gas between the alveoli and red cells was in diffusing across the pulmonary membrane. On the basis of technically difficult studies of the rate at which CO can get into the red cell, and then the combination of these in vitro studies with studies of diffusing capacity in humans, Dr Forster has brought forth quite convincing evidence that not only do we have to think about the resistance interposed by the pulmonary membrane, but an additional resistance, which is just about as great, in getting from the plasma into the red cell Even this resistance, they have sliced still thinner into resistance interposed by diffusing across the wall of the red cell and resistance due to the reaction rate between CO and hemoglobin, once you get inside

This expands our awareness of what is going on as the blood flows through the lung, and although there are technical problems that have prevented getting all this information for oxygen, which of course, would be even more interesting than for CO, they do have preliminary data and a number of indirect ways of looking at the situation This leads them to believe—I don't know why I am speaking for Dr Forster, except that he didn't mention oxygen very much—that the resistance in the case of oxygen thus interposed by the blood is a very significant resistance just as it is in the case of carbon monoxide

To carry all this a step further in an effort to use these techniques to find out what is happening to the size of the pulmonary capillary bed, particularly between rest and exercise, is moving very fast One would certainly expect the diffusing capacity of the pulmonary membrane as an isolated phenomenon, not counting what happens in the blood, to vary in relation to capillary blood volume That is an idea we had before we were aware of some of these complexities, and the ability to test this now carries the matter a good bit further The only trouble is that in getting the resistance due to the diffusing capacity of the pulmonary membrane alone you have to subtract the resistance within the blood itself from the total resistance This subtraction, of course, may have something to do with what you are left with for the pulmonary membrane.

I don't think this alters the general ideas involved, but it does leave me, in particular, in a slightly embarrassing position When we study the diffusing capacity for oxygen, we find that as one exercises, the diffusing capacity for

oxygen goes up, and finally, if one exercises hard enough, approaches a maximal value which does not then increase much if one exercises still harder. We simply explained this to mean that the capillary bed was wide open, and therefore could not open up any more as a result of still further exercise. We believed that this gave a figure related to the size of the total capillary bed

Now, of course, we are not so sure about this, because Dr Forster and his group do not find that the diffusing capacity for carbon monoxide reaches a maximal value When we used carbon monoxide (actually our work has been with the steady state diffusing capacity technique of Dr Filley's) we don't find a plateau either In other words, the diffusing capacity seems to go on increasing linearly So, we are left with considerable agreement with respect to the experimental findings, and don't know what to do with the concept of opening up the entire capillary bed

I am not going to suggest what the physiological explanation is, because the number of variables that now have to be put into the picture—the reaction rate between $O_2$ or CO and hemoglobin, the volume of blood in the capillaries, the hematocrit, the resistance to getting across the red cell wall, and then the changes in the diffusing capacity of the pulmonary membrane during the respiratory cycle and during the cardiac cycle—is getting to be far more than one can balance off and integrate by simple, common sense methods

That is why I am astounded that Dr Forster and his collaborators are able to make these studies during states which are even less steady than those we like to call steady states, and yet I am very much impressed with the degree to which the findings during these "transients," as Dr Forster called them, do seem to run quite close to the more steady state conditions

Well, we are certainly left in the middle of a very complex area, and I can only say that I don't know of anybody who is more likely to make sense out of it in due course than Dr Forster

# Reflexes Originating in the Pulmonary Circulation

*By* GEOFFREY S. DAWES

A FEW YEARS AGO it might well have seemed that little of fundamental interest remained to be learned about reflexes from the lung. The work of Hering & Breuer (*1868*) and of Head (*1889*) had been triumphantly vindicated by Adrian's (*1933*) demonstration of the pulmonary stretch receptors in single fiber preparations of the vagus nerve. Yet even in the *1930's* there were several indications of new and even startling possibilities. Thus, for instance, it was known that intravenous injection of multiple minute emboli into experimental animals caused rapid shallow breathing, which was abolished by cutting the vagi, a phenomenon for which there was then no adequate explanation (Shaw Dunn, *1919;* Whitteridge, *1950*). And on the other hand there was evidence from various sources that serum or certain chemical substances, injected intravenously or inhaled, would cause a profound fall of blood pressure and heart rate, which was abolished or greatly reduced by section of the pulmonary branches of the vagi (Brodie, *1900*). Electrical stimulation of the central ends of these nerves caused either tachycardia or bradycardia, according to the strength of the stimulus employed. During the last 10 years much progress has been made in understanding these phenomena.

## THE PULMONARY DEPRESSOR REFLEX

When the pulmonary arterial pressure, or the pulmonary venous pressure, is raised in cats or dogs, there is a *small* fall of blood pressure and heart rate. This effect is abolished by cutting the vagi. The phenomenon has been verified by all the investigators who have studied it (Churchill & Cope, *1929;* Schwiegk, *1935;* Schweitzer, *1936;* Daly, Ludány, Todd & Verney, *1937;* Parin, *1947;* Aviado et al., *1951*) but the response is, apparently, unreliable. That is to say, it is variable in size and does not appear in every preparation. There is no *certain* indication of the nature or anatomical position of the sensory receptors, though they may be left atrial receptors.

There are now many satisfactory records of impulses in afferent nerve fibers from receptors in the great veins and atria (Amann & Schaeffer, *1943;* Whitteridge, *1948;* Jarisch & Zottermann, *1948;* Dickinson, *1950;* Neil & Zottermann, *1950;* Dawes & Widdicombe, *1953:* Paintal, *1953*, *1955*, *1957;* Coleridge, Hemingway, Holmes & Linden, *1956*). In the cat these end organs are certainly present in the left atrium, but in the dog they occur mainly in the pulmonary veins (Coleridge et al., *1956*). They are of two types. Type A is characterized by the presence of an *a* volley in time with the *a* wave of the venous pressure pulse; these are pressure receptors. The discharge of type B

receptors bears a linear relationship to atrial filling, and Paintal therefore concluded that they are stretch receptors which signal atrial volume distension Some of these fibers cross over to run up in the right vagus, as well as the left

We have here a possible afferent limb for the pulmonary depressor reflex (it is, however, only fair to say that there is no certain evidence that excitation of the left atrial receptors causes a fall of blood pressure and heart rate) Other candidates are pulmonary arterial pressure receptors, whose existence has been very infrequently reported We are on less sure ground when considering the physiological utility of this reflex If the left atrial pressure rises too high, pulmonary edema can ensue So the reflex might be designed to relieve too great a left atrial pressure, by causing peripheral vasodilatation and a fall in cardiac output

## Pulmonary Deflation Receptors

In *1955* Paintal identified certain vagal afferent fibers in the cat's lung, which were sensitized by deflation The method used was unusual In *1951* Dawes, Mott & Widdicombe had shown that injection of various aromatic derivatives of guanidine and isothiourea caused rapid shallow breathing on injection into the right atrium, but not into the left This rapid shallow breathing was abolished by cutting the vagi In an attempt to identify the afferent fibers Paintal noticed that one of these drugs, phenyl diguanide, consistently produced activity in certain otherwise inactive afferent fibers of low conduction velocity, within 3 seconds of the time of injection The localization of the sensory receptors to the lungs was suggested by this very short latent period Subsequent investigation of such fibers showed that they were not excited by inflation of the lungs, but were briefly excited by deflation They were not excited by $O_2$ lack or $CO_2$ excess, but they may be sensitized by pulmonary congestion Injection of a suspension of potato starch, to cause multiple minute embolism, also caused repetitive discharges from these fibers Paintal surmised that phenyl diguanide reached the deflation receptors near the alveoli from the pulmonary capillaries On the present evidence I still feel a slight element of doubt about the name which Paintal has given to these nerve-endings, *deflation receptors* He has shown that they are also excited by cardiovascular changes What is their principal physiological function, to signal changes in the airways or in the circulation? They are quiescent under normal physiological conditions at rest Do they perhaps become active during exercise (which is difficult to simulate in the experimental animal)?

Now injections of amidines (such as phenyl diguanide) and isothioureas give rise not only to rapid shallow breathing but also to a fall in blood pressure and heart rate Part of this fall of blood pressure and heart rate is due to an action on sensory receptors in the lungs, and is abolished by cutting the vagi The question then arises as to whether excitation of pulmonary deflation receptors causes not only rapid shallow breathing but also an effect upon the

cardiovascular system. Until the publication of Paintal's paper I had been fairly certain that the cardiovascular effects of drugs such as phenyl diguanide required the existence of other pulmonary sensory receptors (Dawes & Mott, *1950*; Dawes, Mott & Widdicombe, *1951*; Dawes & Comroe, *1954*), but the evidence is not conclusive on this point We must, therefore, acknowledge the possibility of a certain degree of control of the heart and systemic circulation by means of a reflex arising from receptors in the lung, which can be excited by deflation, by multiple embolism or by drugs

Injection of amidines such as 2 α-naphthyl ethyl isothiourea or phenyl diguanide does not cause any change in pulmonary arterial pressure (Dawes, Mott & Widdicombe, *1951*), nor does it change pulmonary vascular resistance significantly (Barer & Nusser, unpublished) Therefore this reflex does not constitute a negative feedback mechanism for autoregulation of the pulmonary circulation

It is surprising, if indeed it is true, that deflation of the lungs should cause a reflex fall of systemic blood pressure and heart rate, yet this suggestion fits well with some interesting new evidence

## Tachycardia and Anoxia

Anoxic anoxia causes an increase in heart rate, and this has been thought by some to be due to stimulation of aortic and carotid chemoreceptors However Heymans, Bouckaert & Dautrebande (*1931*) showed that when the carotid body was excited by intravenous injection of various drugs, the heart rate decreased Recently Daly & Scott (*1958*) have analyzed the cause of anoxic tachycardia They showed that in dogs whose lungs were artificially ventilated, perfusion of the carotid bodies with anoxic blood caused a profound *fall* of heart rate But in dogs breathing spontaneously there was an increase, a decrease or no change in heart rate Their experiments suggested that the cardio-accelerator response was due to a "stretch reflex from the lungs resulting from the increased depth of breathing (Anrep, Pascual & Rossler, *1936*)," and was abolished by severing the pulmonary branches of the vagi The tachycardia of anoxia was thus attributed to a reflex, arising from pulmonary receptors, and excited by hyperpnoea Here we may have the inverse image of Paintal's hypothesis, a reflex increase in heart rate caused by hyperpnoea, in place of a reflex fall in blood pressure and heart rate induced by deflation of the lungs There is no evidence to show whether the sensory pathway is the same

## Reflex Control of the Pulmonary Circulation

Finally, I cannot resist a word or two about reflex control of the pulmonary circulation Most investigators now admit the fact that the pulmonary blood vessels have tone, and therefore the possibility that this tone can be altered For many years I de Burgh Daly has sought, and found, evidence in the anesthetized dog that the pulmonary vascular resistance can be controlled by extrinsic vasomotor nerves Both vasoconstrictor and vasodilator responses have

been demonstrated in preparations designed to eliminate the passive effects of changes in pulmonary flow, in ventilation, and in the tone of the bronchial muscles, bronchial vessels or systemic arterial pressure (through communicating channels) Recently Daly & Daly (*1957*) have produced direct evidence that stimulation of the carotid body chemoreceptors (by perfusion with venous blood) causes a *decrease* in pulmonary vascular resistance. This response was abolished by cutting the carotid sinus nerves or the cervical vago-sympathetic trunks or by administration of atropine It was concluded that the efferent arc of this reflex was mediated by vagal cholinergic nerve fibres Here at long last is direct evidence in the experimental animal for reflex control of the pulmonary circulation There is one word of caution however, which Daly & Daly add, that they were unable to designate the vascular territory involved in the vasodilatation

## Conclusion

In these few minutes I have briefly mentioned a number of complex mechanisms It is clear that we do not yet understand them fully, but I would suggest one conclusion to which in the future we may be led, namely, that the pulmonary circulation is by no means the passive vehicle for blood flow which some have supposed The pendulum swings and the evidence now points the other way, towards a dynamic control of the pulmonary blood vessels, and towards some degree of reflex control of the heart and systemic circulation by sensory receptors within the lungs

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## Conclusion

In these few minutes I have briefly mentioned a number of complex mechanisms. It is clear that we do not yet understand them fully, but I would suggest one conclusion to which in the future we may be led, namely, that the pulmonary circulation is by no means the passive vehicle for blood flow which some have supposed The pendulum swings and the evidence now points the other way, towards a dynamic control of the pulmonary blood vessels, and towards some degree of reflex control of the heart and systemic circulation by sensory receptors within the lungs

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In using the calculated resistance to study the effects of a stimulus on the pulmonary vessels, a change in this number has been frequently equated to a change in vessel tone. But since the quantities used in the calculation are continually varying, it is probable that the tone is more closely related to the instantaneous resistance to flow. By this reasoning, the mean resistance obtaining in any finite period is that defined by equation (3)

$$R_M = \frac{1}{T}\int_0^T R_t dt = \frac{1}{T}\int_0^T \left\{\frac{PA_t - LA_t}{Q_t}\right\} dt \qquad (3)$$

where $R_M$ = mean pulmonary vascular resistance

$R_t$ = instantaneous pulmonary vascular resistance

Equations (2) and (3) are obviously dissimilar. By equating the two expressions it can be demonstrated that the calculated and mean resistances will be equal only when the resistance is constant or the rate of flow is fixed. Since the realization of either condition is unlikely, the calculated and mean resistances will probably never be exactly the same.

The practical importance of this inequality is uncertain, since the measurements necessary for the calculation of mean resistance cannot be made. But this analysis serves to remind us that changes in the calculated resistance must be interpreted with caution. Although this number is a useful tool for studying the pulmonary vessels, it can probably not be used for assessing alterations in tone in any exact way.

A second difficulty encountered in studying the pulmonary circulation is known to have practical importance. It concerns the multiplicity of factors unrelated to the tone of the vessels which can influence the calculated resistance to flow. Dr. Burton has already talked about these factors. Among the factors which can be monitored when studying human subjects are those listed in table 1.

TABLE 1.—*Factors Other Than Vascular Tone Which Can Affect the Relation Between Pressure and Flow in the Pulmonary Vessels*

(1) Rate of pulmonary blood flow
(2) Heart rate
(3) Pressure in the left atrium
(4) Constriction or dilatation in the systemic circulation
(5) Extra vascular pressure within the alveoli and thorax
(6) Central blood volume

Of all of the listed factors, the most troublesome is the rate of pulmonary blood flow. The effect of this variable on the pressure-flow relation is shown in the curve in figure 1. This curve was sketched by using data obtained from two types of studies. In the first, the pressures and flow in the pulmonary circulation were measured in patients who had undergone pneumonectomy,[1] and in the second, the same variables were measured in normal subjects in whom the blood flow through one lung had been temporarily stopped.[2,3] In both studies, the flow through one lung approximately doubled, yet the pulmonary arterial pressure increased less than 50 per cent. On the assumption that the left atrial pressure was not greatly altered, these data indicate that when

# Physiological Factors Regulating Pressure, Flow and Distribution of Blood in the Pulmonary Circulation

*By* Harry W. Fritts, Jr., and André Cournand

There is little doubt that the tone of the peripheral arterioles plays an important part in regulating the resistance to blood flow in the systemic circulation. Whether the small vessels of the lungs exercise similar control over the pulmonary vascular resistance is less certain. Many physiologists who have studied the pulmonary vessels have concluded that these vessels lack the capacity to dilate and constrict. Hence, with the importance of tone uncertain, the control of the pulmonary circulation has remained a matter of debate.

The purpose of this presentation will be to review the evidence that tone plays a role in regulating the pulmonary vascular resistance. The discussion will be limited to observations made in normal man. First, the methods which have been used to study the problem will be examined, then the evidence for constriction and dilatation will be presented and assessed.

## Examination of Methods

Most studies of the human pulmonary circulation have entailed the measurement of three variables: (1) the pressure in the pulmonary artery, (2) the pressure either in the left atrium or at the end of a wedged catheter and (3) the rate of pulmonary blood flow. With these variables the pulmonary vascular resistance has been calculated. This calculation is shown below.

$$R_C = \frac{PA_M - LA_M}{Q_M} \qquad (1)$$

$R_C$ = calculated pulmonary vascular resistance
$PA_M$ = mean pressure in the pulmonary artery
$LA_M$ = mean pressure in the left atrium
$Q_M$ = mean rate of volumetric blood flow

A more general form of this relation is shown in equation (2)

$$R_C = \frac{\frac{1}{T}\int_0^T PA_t dt - \frac{1}{T}\int_0^T LA_t dt}{\frac{1}{T}\int_0^T Q_t dt} \qquad (2)$$

$PA_t$ = instantaneous pressure in the pulmonary artery
$LA_t$ = instantaneous pressure in the left atrium
$Q_t$ = instantaneous rate of volumetric blood flow
$T$ = length of the finite period over which the measurement is made

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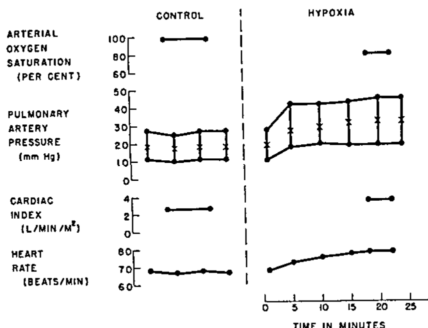



Fig 2.—Effect of acute induced hypoxia on the arterial oxygen saturation, pulmonary artery pressure, cardiac index, and heart rate The study was performed on a man believed to have a normal pulmonary circulation

ture of 12 per cent oxygen in nitrogen for 20 minutes, his arterial blood oxyhemoglobin saturation had fallen from 98 to 68 per cent During the same period, the mean pulmonary arterial pressure had risen to almost twice the resting value Further, the cardiac output, the heart rate, and the ventilation were moderately augmented, while the pulmonary wedge pressure, the brachial arterial pressure and the central blood volume were not changed

The interpretation of the data is complicated by the fact that several varibles were altered Apart from the pulmonary hypertension, the most important of these changes was the 35 per cent increase in flow According to the curve in figure 1, however, this increase was not sufficient to account for the rise in the pulmonary arterial pressure Hence, it seems reasonable to believe that hypoxia constricted the vessels of the lungs

Similar observations led von Euler and Liljestrand[9] to suggest that localized hypoxia might play a role in the distribution of the total pulmonary blood flow They postulated that in hypoxic areas the vessels would be constricted, and that part of the blood normally flowing through these channels would be shunted through vessels in other, better aerated parts of the lungs This hypothesis has been tested in both man[10] and animals[11 15] by allowing one lung to breathe an hypoxic mixture Although the results have been conflicting, most suggest that constriction takes place in the vessels of the hypoxic lung

In most of the studies which have been carried out with unilateral hypoxia, a number of assumptions have been necessary In order that these assump-

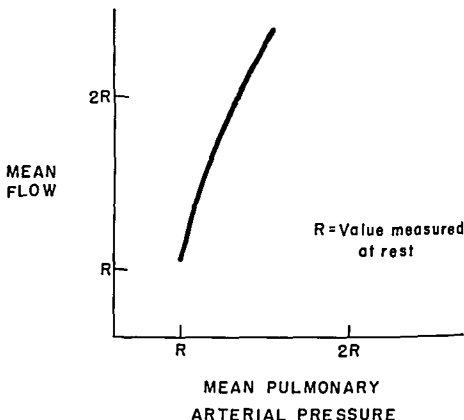



Fig 1—Schematic drawing of the relation between mean pulmonary arterial pressure and mean flow in the pulmonary circulation of normal man

the cardiac output increases to twice the resting value, the calculated vascular resistance concomitantly falls

In summarizing these remarks on methodology, three points can be made (1) The calculated resistance is a useful tool for studying the tone of the vessels, but it will probably not reflect an alteration in tone in a precise way. (2) Constriction or dilatation can be suspected whenever a stimulus displaces the pressure-flow point from the general area of the curve in figure 1 (3) When such a displacement has been effected, it is necessary to consider the possibility that one of the factors listed in the table caused the displacement to occur Only after this possibility has been excluded is it reasonable to assume that there has been an active change in tone

## Evidence for Vasoconstriction

The response of the human pulmonary vessels to acute, induced hypoxia provides strong evidence that these vessels can constrict [4 8] Such a response is shown in figure 2

These results were obtained from a study performed on a man, age 35, who was believed to have a normal pulmonary circulation After breathing a mix-

Eight patients believed to have normal hearts and lungs were studied Each breathed into a mouthpiece for two 20 minute periods, separated by a 15 minute interval of rest In one period, 21 per cent oxygen in nitrogen was administered, and in the other, a mixture of 12 per cent oxygen in nitrogen was supplied In each of these periods, pressures and flow were measured, then acetylcholine was infused into the main pulmonary artery at the rate of 5 mgm. per minute. During the infusion the measurements of pressure and flow were repeated The results of one of the studies are shown in figure 3

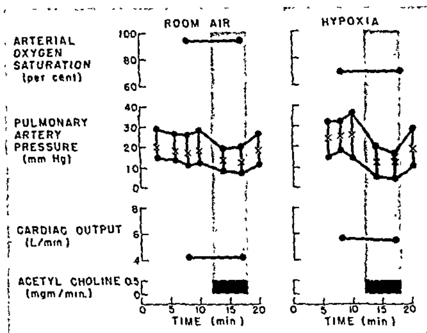



FIG 3.—Effect of acetylcholine and acute induced hypoxia on the arterial oxygen saturation, pulmonary artery pressure, and cardiac output. The study was performed on a man believed to have a normal pulmonary circulation

It can be seen that while room air was breathed, acetylcholine lowered the pulmonary arterial pressure while the cardiac output was not altered During hypoxia, pulmonary hypertension developed and acetylcholine had a more evident effect This striking fall was not seen in every subject, but in almost all some reduction in pressure was observed

Acetylcholine did not affect the ventilation, the pulmonary wedge pressure, the central blood volume, or the brachial arterial pressure Moreover, in most instances, the cardiac output stayed constant, in a few it was slightly increased These observations led us to conclude that the effect of acetylcholine was limited to the pulmonary circulation and that the drug actively dilated the vessels of the lungs

Finally, the pathways whereby the effects of hypoxia and acetylcholine are mediated have not been identified It appears that one possibility can be elimi-

tions might be avoided, Dr. Alfred Fishman and other members of our laboratory developed a method which combined bronchospirometry, cardiac catheterization and arterial cannulation[16] The bronchospirometry tube provided a means for measuring the gas exchange in each lung separately, while the catheter and cannula made it possible to analyze the composition of samples of mixed venous and arterial blood

When concentrations of oxygen as low as 10 per cent were administered to 1 lung in 6 human subjects, there was no evidence that unilateral hypoxia caused a re-partition of the total pulmonary flow.[16] But when in a more recent study, 4 per cent oxygen was administered to one lung in a group of 6 subjects, unilateral constriction appeared to occur in 4.[17] In the fifth subject, nothing happened, but in the sixth, pulmonary hypertension developed without a change in the distribution of flow Hence, the mechanism proposed by von Euler and Liljestrand does not appear to be invariably effective Further, the response has been elicited only when the degree of hypoxia has been severe

Eight patients believed to have normal hearts and lungs were studied Each breathed into a mouthpiece for two 20 minute periods, separated by a 15 minute interval of rest. In one period, 21 per cent oxygen in nitrogen was administered, and in the other, a mixture of 12 per cent oxygen in nitrogen was supplied In each of these periods, pressures and flow were measured, then acetylcholine was infused into the main pulmonary artery at the rate of .5 mgm per minute. During the infusion the measurements of pressure and flow were repeated The results of one of the studies are shown in figure 3.

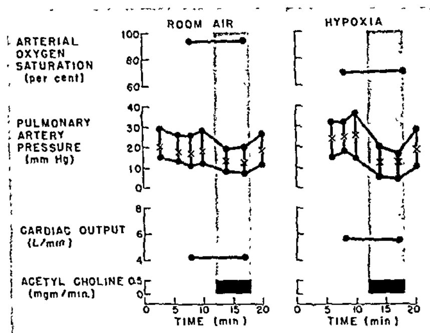



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nated on the basis of two studies which we have performed In the first, Dr Fishman demonstrated that hypoxia produced pulmonary hypertension in a woman in whom the cervical and upper thoracic sympathetic ganglia had been resected[8] In the second, we demonstrated that hypoxia raised and acetylcholine lowered the pulmonary arterial pressure in a man in whom all the sympathetic ganglia had been removed.[18] It appears, therefore, that these ganglia are not essential for the mediation of either effect

## Summary

The methods customarily used to study the tone of the human pulmonary vessels have recognized limitations Even so, the experimental evidence indicates that these vessels can dilate and constrict. But these two functions have been demonstrated only under extreme conditions Hence, the role played by tone in controlling the pulmonary circulation under normal conditions is not, as yet, clear

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## Discussion

Söderholm The effect on the pulmonary circulation produced by acetylcholine in artificially induced hypoxia ought to be demonstrable also in cases

with spontaneously occurring hypoventilation In such cases the effect on the pulmonary arterial pressure might be limited if the hypoventilated area comprises only a fraction of the total lung volume. Here, a more pronounced effect could be expected on the arterial oxygen tension or saturation because of a change in ventilation-blood flow relationships This is under the assumption that no effect occurs on the pulmonary ventilation If no effect of the acetylcholine infusion is demonstrable on systemic blood pressure, this assumption seems to be valid as shown by Fritts and associates We have had the opportunity to investigate a patient with a pericardial cyst which compressed part of the left lower lobe. Otherwise this patient had no disease of the lungs or cardiovascular system demonstrable clinically or by extensive cardiopulmonary function tests

The patient was studied during heart catheterization both at rest and during light exercise All studies were performed in a steady state both before and during continuous infusion of about 8 mg acetylcholine/min Neither the pulmonary arterial pressure nor the systemic pressure were significantly altered The cardiac output remained essentially the same both before and during the infusion The arterial oxygen saturation, however, showed a marked decrease during acetylcholine infusion both at rest and during exercise (11 per cent and 9 per cent respectively). At the same time the heart rate increased, possibly because of the rather pronounced hypoxaemia

This case demonstrates that acetylcholine causes vasodilation in the lesser circulation when regional hypoventilation of the lungs exists in a patient with otherwise healthy lungs and cardiovascular systems

CHAIRMAN COMROE: Dr Dexter, do you have any information from your studies on patients before and after surgical relief of mitral stenosis as to the time course of decrease in pulmonary vascular resistance and whether this time course gives any clues as to whether the resistance is due to vasoconstriction or to organic narrowing?

DEXTER: No, really, except that two weeks after surgery there can be a dramatic fall in pulmonary vascular resistance, particularly if it had been very high preoperatively When the resistance is only moderately increased preoperatively, the immediate postoperative fall is much less dramatic

CHAIRMAN COMROE Has anyone observed a decrease of resistance between zero time and two weeks?

DEXTER No

CHAIRMAN COMROE So it might occur much more quickly than that?

DEXTER It might, and we plan to leave a catheter in the pulmonary artery during surgery and find out how fast the pressure falls after the mitral stenosis is relieved I am not aware of this having been done

I would like to ask Dr Fritts a question There is one factor other than those he listed which can affect the calculated pulmonary vascular resistance, and that is a change of pulmonary blood volume He mentioned that he had measured it and that it had remained unchanged in his experiments However, I wonder if he has any information as to how much of a change in pulmonary

*blood volume is necessary to produce a change in pressure, flow and resistance* relationships? In other words, is it a matter of a few cu cm. or many cu cm.?

If a patient lying on the table raises his feet about 10 inches above the level of the table, pressures in the pulmonary artery and wedge position rise 5 mm Hg or more in the normal, and the pressures tend to come drifting back to normal in about one-half minute I assume that this is due to a redistribution of blood from the legs into the thorax. These changes are too rapid for measurement of changes in resistance, but certainly if blood does enter the thorax, the vessels presumably become more distended, and the pressure, flow and resistance relationships become altered, as Dr Burton and Dr Sarnoff have emphasized I would like Dr Fritts to comment on the possibility of such a shift in intrathoracic blood volume in his experiments

FRITTS I cannot answer your question about the relation between the pressures in the pulmonary vessels and the size of the central blood volume. I can, however, give you some information about the reproducibility of the measurement of this volume when estimated by the Stewart-Hamilton technique

We made two successive measurements of the central volume in 8 normal *subjects who were resting quietly. We found that the standard deviation of the* differences between each pair of measurements was 9 per cent of the mean Two standard deviations would represent, therefore, about 200 cc of blood in a man of average size In the face of such wide variation in resting subjects, it seems doubtful that this method is suitable for measuring small changes in the volume of blood in the thorax

As an alternative method, we used a tilt-table similar to that described by Dr Fenn and his associates The table was quite sensitive to a change in the relative weights of the two ends of the body, and a variety of vasoactive drugs caused such changes to occur We were particularly interested in the effect of acute hypoxia In a series of 10 patients, no effect was observed

WOOD Dr Fritts, I should like to ask you these questions Were your control subjects normal individuals? Was there no increase in depth of respiration? I know that the rate of respiration was unchanged Second, did the arterial oxygen saturation fall 2 or 3 per cent? Third, were these patients under some sort of premedication? Did they have barbiturates as well as a catheter?

FRITTS To answer these questions in reverse order, no premedication was given The patients were basal and had fasted overnight.

In regard to the arterial oxygen saturation, the largest variation was 3 per cent On the average, there was no change

Neither the respiratory frequency nor the tidal volume was affected by acetylcholine

The patients had different diagnoses Each was convalescent and was believed to have a normal pulmonary circulation

BURTON I would like to say, following the discussion of Dr Fritts, that many people in their interpretation of changes of resistance, whether they are active or passive, make it much more difficult than it has to be

After all, what I am going to say is based on a perfectly respectable theorem of scientific philosophy The fact of the matter is that the vessels cannot 'know' what is happening anywhere else. There are only three things that affect them: one is the transmural pressure between the inside and the outside; the other is the tension in their wall, which may be partly passive due to elasticity and also 'active' due to smooth muscle; the third factor is their size Of course, there is a relation between these three things which must exist. If one knows what has happened to the transmural pressure, or what has happened to the size, which one can calculate from the change of resistance, then one can deduce what happened to the tension in the wall. Then one can often decide whether the change was passive or active

If the resistance went up and the blood pressure went down, that might be 'passive' Therefore, it seems to me useful to put one's self in the position of the blood vessel under consideration The only thing that can change the size of the vessel is a change in these variables transmural pressure and tension on the wall I think that many make it much more difficult than it has to be.

CHAIRMAN COMROE Were you going to propose a way for measuring all of these things in man?

BURTON One can make a reasonable guess as to whether a change in resistance is active or passive

From the wedge pressure and the pulmonary artery pressure, you know if the arteriolar pressure has gone up or down You know what has happened to the size of the vessels, if you calculate your resistance correctly, which not all people do So I think that in most of these problems you have enough to have a definite answer Of course, there are some cases where it turns out that you cannot be sure

SARNOFF I think that one of the most intriguing things mentioned this morning is Dr Dexter's observation on the rise of pressure in the pulmonary artery Could it have resulted from a change in intrathoracic pressure?

DEXTER It may be, as you say a change in intrathoracic pressure Certainly when the subjects lift their legs they tighten their abdominal muscles When the feet rest on a support, the musculature relaxes, but it is possible that there still may be a shift of the abdominal viscera headwards, a rise of the diaphragm, and rise of intrathoracic pressure on this basis These have been casual observations on our part.

FORSTER. We have been interested in the relationship between the blood flow and the diffusing capacity One aspect of this relationship which intrigues me a great deal is the difference between the changes in the diffusing capacity for oxygen and those for the diffusing capacity for CO, with exercise or increase in cardiac output At the moment I rather suspect the explanation lies in the chemical reactions of the red cell with $O_2$ and CO Dr Norman Staub and Dr John Bishop have developed a very elegant apparatus for measuring the rates of uptake of $O_2$ by red cells and we hope to have some answers on this in the next six months

I would like to mention one other sub-question which is always in my mind, and that concerns the anatomical site of the major vascular resistance in the

lungs I am not sure just where everybody thinks it is Apparently it is not always in the capillary bed We have, for example, seen patients who had a normal diffusing capacity, which implies a normal capillary bed, and at the same time, a raised pulmonary artery pressure We have also seen patients, of course, with raised pulmonary artery pressure, plus damage to the capillary bed Too often, I think, we equate any changes in the vascular resistance with damage to the capillary bed and I suspect that the capillary bed is not the major source of the vascular resistance in the lungs

CHAIRMAN COMROE Before you get off the subject of the maximal diffusing capacity, Dr Forster, it seems to me that Dr Riley's concept is a very important one It would be very helpful if we knew something about the surface area of the capillary bed at rest, whether it can increase, or whether the bed is essentially a fixed one The concept of maximal diffusing capacity or just of whether the diffusing capacity can increase at all is a very important one in this respect, especially in patients with cardiopulmonary disease

In view of the curve that Dr. Fritts showed of pressure and flow through the pulmonary vascular bed, do you believe that there is a limit to increase in surface area of pulmonary capillaries in contact with ventilated alveoli?

It is obvious from the pressure and flow measurement that there is a period in which flow can increase considerably—two or possibly three times—with little increase in pressure, this presumably comes about by an increase in the vascular bed, including possibly an increase in the size of open capillaries or an opening of previously closed vessels

There must come a point at which they reach their practical limit of distensibility and then an increase in flow is achieved largely by an increase in pressure rather than by further dilatation At this point, the diffusion capacity should rise less steeply as pressure increases How would you interpret diffusion studies in light of these curves?

FORSTER I think there is no question that eventually there is a limit to a man's diffusing capacity as pulmonary blood flow rises

The fact that pulmonary pressure (or resistance) does or doesn't rise as pulmonary blood flow increases, does not necessarily indicate changes in the pulmonary capillaries because the resistance may not be in the capillary bed at all If blood flow and diffusing capacity are measured at increasing levels of exercise a limit will be reached eventually and I expect the curve would have a flat top or plateau just as Dr Riley has found Unfortunately, because of the poor health of individuals in Philadelphia, we haven't gotten to that high a blood flow, and apparently, I believe, only the Swedes work that hard However, we have some visitors in Philadelphia who may run this hard, and perhaps we will find the plateau At the moment, up to a cardiac output close to 18 or 19 L/min, we have not seen any indication of a plateau at the top, which indicates to me the pulmonary capillary bed has simply not been adequately strained by these levels of cardiac output

BURTON I wanted to see whether I could bring Drs Riley and Forster down to earth from the clouds of calculations of diffusion of oxygen in the blood

stream and into the red cell, down to the solid earth of a realistic view of blood flow in the capillaries

After all, what do they mean by diffusion through the blood *stream*, when the lung capillaries are just about the size of the red cell

There isn't any "stream" in the capillaries It is like oysters going down one's esophagus I am very sure the red cell isn't its usual discoid shape at all in going through the capillaries, so what do they mean by the diffusion "in the blood stream" and "across the red cell"? I wouldn't be surprised if the red cell was considerably churned up inside as it goes along. I wonder what real validity such calculations of diffusion into a red cell have, in this problem of diffusion in the lung capillaries

CHAIRMAN COMROE Dr. Dexter, don't you believe there is evidence that there is actually axial streaming in the pulmonary capillary from your experiments on the hematocrit of pulmonary blood?

DEXTER There is good evidence, indeed, that there is a change in the pulmonary hematocrit and therefore axial streaming in the small pulmonary vessels, but I don't think this bears on the oyster problem

In small blood vessels of the systemic circulation, turbulent flow exists in the sense of random distribution of the red cells in the stream, even though the Reynold's number is very low It is not turbulent in terms of the Reynold's number but turbulent in the sense of random distribution of the red cells at very low flow rates I agree with Dr Burton that in the systemic capillaries, red cells are just squeezing through The pulmonary capillaries are much bigger, however, than most of the systemic capillaries

CHAIRMAN COMROE Dr Riley, has Dr Burton brought you down to earth?

RILEY I have been up in the clouds all right, but not so much in this particular area This is Dr Forster's area of celestial thinking There is just one thing which would bring me definitely down to earth, namely, if somebody could turn up a blood disease, a red cell disease, which looks like a diffusional difficulty in the lung, because this might lead us to a very valuable distinction between the things that we believe to be going on within the blood and those which are going on in the pulmonary membrane

FORSTER If you compare the reaction rates of $O_2$ or CO with the reduced Hb solutions, where the Hb molecules are exposed to the gas molecules right in the vicinity, with the reaction rates when the red cells are exposed to the same gas tensions, you will find the latter to be many times slower This is because the high concentration of the Hb in the red cell mops up the $O_2$ or CO in the more superficial portions of the cell, decreasing the gas pressure gradient and slowing the overall process

Now, as to a disease of the red cells affecting lung gas exchange, Dr Elizabeth Gerst in New York as well as our own group are investigating this possibility There is one common condition of this sort right under our noses, and that is anemia In anemia the diffusing capacity for CO is less than normal, presumably because there is a decrease in the amount of hemoglobin which is available in the capillary bed to combine with the gas. The rate of CO uptake depends largely on the rate at which CO can react with the red cells

I assume the diffusing capacity for $O_2$ also decreases in anemia although I am not aware that anybody has ever actually made the measurements.

CHAIRMAN COMROE. Dr. Burton, I have a mental image of photographs published by Parker and Weiss many years ago, in which it was shown that in mitral stenosis there were capillaries in the lungs with 4 or 5 red blood cells abreast

BURTON I was interested in the electron microscope picture you showed us. It seemed to me that those capillaries were much wider than I thought lung capillaries to be The red cells had lots of room on the inside, didn't they?

CHAIRMAN COMROE · I cannot say That was made by Dr. Low of Louisiana State (Anat Rec *117*:241-264, 1953).

BURTON My point is that calculations made on discoid red cells are simply academic in this connection. To me it doesn't have anything to do with these oysters going down the esophagus The red cell isn't in a stream any more, and its wall is actually in contact with the capillary wall I don't see how the calculation made in connection with the red cells in free suspension can have anything to do with this diffusion resistance in the red cell in a capillary.

# III. THE PATHOLOGY OF THE PULMONARY CIRCULATION

CHAIRMAN: JESSE E. EDWARDS
CO-CHAIRMAN: WILLIAM B. WARTMAN

## Classification of Pulmonary Hypertension and Anatomy of the Postnatal and Fetal Pulmonary Vascular Bed

*By* JESSE E EDWARDS

IT IS FITTING that this conference on pulmonary hypertension has included in it a panel on pathology In the first place, pulmonary hypertension may be categorized on structural grounds in such a way as to make the classification useful from the functional and clinical points of view In the second place, the basis for elevation of pulmonary blood pressure frequently and perhaps always depends on morphologic alterations

This paper will present a classification of chronic pulmonary hypertension and also will describe the essential anatomic features of the various segments of the normal pulmonary vascular bed The parts of the paper will serve as points of departure for the three clinical panels to follow and as specific reference points for certain presentations in both this panel and those to follow

### CLASSIFICATION OF PULMONARY HYPERTENSION

The term "pulmonary hypertension" usually implies "pulmonary arterial hypertension " In some conditions, elevation of pulmonary venous pressure accompanies pulmonary arterial hypertension In other conditions the pulmonary venous pressure is normal

The pulmonary arterial blood pressure depends on the volume of blood flow, per unit of time, through the arteries and on the resistance to that flow It is theoretically possible for the pressure to increase in the presence of normal resistance if the flow is very greatly increased As a practical measure, however, when pulmonary hypertension occurs there is nearly always increased resistance to flow In some instances the volume of blood flow may be in excess of normal, while in many it is either normal or below normal In view of the foregoing considerations it becomes apparent that a classification of pulmonary hypertension may readily be expressed in terms of increased

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CHAIRMAN COMROE: Dr Burton, I have a mental image of photographs published by Parker and Weiss many years ago, in which it was shown that in mitral stenosis there were capillaries in the lungs with 4 or 5 red blood cells abreast.

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tolic pressure is transmitted to the pulmonary arteries. In atrial septal defect such transmission of pressure is not possible

In uncomplicated atrial septal defect the pulmonary vascular resistance is low or normal so that in spite of large volumes of pulmonary blood flow the pressure is not elevated It is only as a result of complicating obstructive lesions in the pulmonary arterial and arteriolar bed that the pulmonary vascular resistance (and pressure) rises in atrial septal defect

The term *pulmonary disease* as used here includes chronic parenchymal disease resulting in loss of functioning pulmonary substance, and it includes various obstructive lesions of the pulmonary arterial and arteriolar bed The vascular lesions result from pulmonary embolism, possibly from thrombosis of small pulmonary arteries, from idiopathic intimal proliferation, and from various forms of arteritis

When pulmonary hypertension occurs on the basis of pulmonary disease the site of elevated resistance varies with the specific condition It may lie at arterial, arteriolar or possibly capillary levels

## Anatomy of the Pulmonary Vascular Bed

The normal postnatal pulmonary vascular bed has anatomic qualities which correspond with the fact that functionally it is a low resistance system Moreover, the fact that the small arteries and the arterioles are equipped with little muscle is supportive of the fact that only very low ranges of vasoconstriction are possible in this part of the circulatory system under normal circumstances

The major pulmonary arteries and their branches that accompany the cartilaginous bronchi are elastic arteries They are characterized by medial layers that have many laminations of elastic tissue and that in a general way may be said to bear some resemblance to the medial layer of the aorta That important differences in detail exist in this layer, depending on the category of pulmonary hypertension, will be brought out in Dr Heath's presentation in this panel The elastic arteries branch to form the muscular arteries The latter are characterized by their medial structure The media is composed of a circular layer of smooth muscle bounded by external and internal elastic laminae The structure of the normal pulmonary muscular arteries stands in contrast to that of the systemic arteries of comparable caliber by virtue of the thin media of the former Muscular arteries of the lung vary from about 100 to 1000 microns in diameter The largest ones accompany bronchioles while the smallest accompany alveolar ducts

The arterioles branch from the small muscular arteries and primarily accompany the alveolar sacs The proximal part of the normal arteriole shows a structure qualitatively like that of the muscular artery from which it arises Here the arteriole is equipped with a thin muscular media This gives way to a pattern in which no identifiable muscle is present Beyond the level at which a muscular media is present the arteriolar wall is composed of lining endothelium, a small amount of supporting collagen, an elastic layer and a thin collagenous adventitia

pulmonary vascular resistance, which may result either from obstruction of blood flow by structural lesions or from reduction in the amount of functioning pulmonary tissue

The following conditions cause or are associated with increased pulmonary vascular resistance

1 Obstruction to venous flow
2 Congenital septal defects of the heart or great vessels
   a) Unobstructed communication between the ventricles or the great arteries
   b) Interatrial communications
3 Pulmonary diseases
   a) Parenchymal
   b) Vascular

Further presentations in this panel and in those to follow will define in detail the functional and structural characteristics of the foregoing types of pulmonary hypertension However, a few introductory remarks about each may be appropriate here

*Obstruction to pulmonary venous flow* is caused by many conditions, acquired or congenital Common acquired conditions are mitral stenosis or insufficiency and elevation of left ventricular diastolic pressure, as in chronic left ventricular failure. Congenital conditions include various disturbances of the mitral valve, endocardial sclerosis of the left ventricle and stenotic lesions of the pulmonary veins

It is only in this category of pulmonary hypertension that there is elevation of pulmonary venous and capillary pressure In the remaining two categories the pressures in the pulmonary veins and capillaries are normal unless, by chance, there is a coincidental element of obstruction to pulmonary venous flow When there is obstruction to pulmonary venous flow, two zones of high resistance exist One lies at the site of the primary lesion, and the other at the pulmonary "arteriolar" level

Not all *congenital septal defects* of the heart or great vessels are associated with pulmonary hypertension When communications exist between the ventricles or the great arteries the important distinction revolves about the size of the communication When such an opening is small the pulmonary circulation is protected from the left ventricular pressure by the obstructive character of the small opening, and the pulmonary arterial resistance and pressure are not elevated When, on the contrary, the opening is large enough not to have an obstructing quality, the left ventricular systolic pressure is transmitted to the pulmonary arterial system The volume of pulmonary blood flow varies inversely with the level of pulmonary vascular resistance. Resistance varies considerably from case to case, but in each it is increased to a degree at the arteriolar level

In any consideration of the dynamics in patients with cardiac septal defects the condition, atrial septal defect, on the one hand, must be kept separate from ventricular septal defect, patent ductus arteriosus or functionally related conditions, on the other hand In large ventricular septal defect or functionally similar conditions the anatomic arrangement is such that left ventricular sys-

# Relation of Bronchial to Pulmonary Vascular Tree

*By* A. A. LIEBOW, M. R. HALES, AND W. E. BLOOMER

THAT THE LUNGS have a double source of blood must be considered in the attempt to understand the total economy of the pulmonary circulation. Normally, the "private," or bronchial circulation is relatively small as contrasted with the pulmonary arteries and veins, which are in the "public" service of gas exchange for the body as a whole. In the absence of disease, precapillary connections between the two systems are difficult to demonstrate and are believed by many to be only by means of capillaries, in the region of the respiratory bronchioles.[1]

In disease, there are at least two general conditions when the bronchial circulation is stimulated to expand: (1) when new tissue is formed and (2) when the pressure in the pulmonary arteries is diminished. For convenience in this discussion, "bronchial arteries" will refer to all systemic arteries that supply or become related to the lungs.

## RELATIONS OF PULMONARY AND SYSTEMIC ARTERIES

### *Anatomic Observations in Man*

Localized congenital communications between systemic and pulmonary arteries in the absence of heart disease occur with extreme rarity. Branches of intercostal and internal mammary arteries may, however, cross into the lung within reflections of the pleura to become confluent with the branches of the pulmonary arteries. Such congenital communications may be associated clinically with murmurs and appear as contorted shadows radiographically. They do not, however, produce the cyanosis, polycythemia, clubbing or other changes characteristic of the much more common pulmonary arteriovenous fistulas, although they may rarely be involved and add to the complexity of the latter.[2,3]

In organizing pulmonary disease, especially in bronchiectasis, and to a lesser degree as in such conditions as tuberculosis, in which ultimate hyalinization of granulation tissue is more extensive, the bronchial arteries expand remarkably while the pulmonary arteries become diminished.[4,5] Within diseased portions of the lung, as demonstrated in vinylite casts, the two tend to approach each other in internal diameter and precapillary anastomoses that may exceed 1 mm in diameter, now develop between the two arterial systems[6] (fig. 1). The stimuli to the development of collateral circulation in the diseased lung are only dimly understood, but may be associated in part with obstruction of distal distributions of the pulmonary arteries, in part with the development of new capillaries as granulation tissue from the bronchial vessels, and in part to meet the need for oxygenated blood of newly formed lymphoid tissue and

While the arterioles and arteries closely accompany the air passages, the venules and veins, on the contrary, are as far from the air passages as they can be and yet be related to their particular parenchymal units.

The venules resemble the nonmuscular parts of the arterioles. The venous trunks formed by their confluence show distinct medial layers In contrast to the media of the muscular arteries, which has a compact circular layer of muscle, the media of the veins has irregularly disposed bundles of muscle separated by connective tissue

It is of interest to mention the important features of the fetal pulmonary vessels since fetal characteristics persist in the pulmonary vascular bed in some types of pulmonary hypertension. The fetal muscular arteries and the proximal segments of arterioles have a thick medial layer and a correspondingly narrow lumen In the first few weeks after birth the media gradually thins and the lumen widens By the age of 6 months, and often by the age of 2 months, the normal adult pattern already described has been reached.

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FIG 1 —Cast of bronchus and vessels in bronchiectasis In the wall of a large bronchiectatic sac is seen a greatly enlarged bronchial artery (black) which approaches in size the pulmonary artery at the same level (grey), at "An" there is a large anastomosis between the two The functional implications of these anastomoses in disease are discussed in the text

muscle common in such conditions as bronchiectasis, the forces operating to meet this "need" are obscure

Other newly formed tissues, such as neoplasms, whether primary or metastatic, also have been found to receive their blood supply from systemic arteries,[4 7,8] although some have claimed that the latter are nourished by blood from the pulmonary arteries[9]

When pulmonary arterial pressure is diminished the bronchial arteries enlarge and may even substitute for absent pulmonary arteries[10,11] In pure pulmonic stenosis, the increase is only slight or moderate, even in patients who have survived into their middle forties In tetralogy of Fallot, however, the expansion is much greater, possibly because of the higher prevalence in this condition of thrombosis associated with the polycythemia Here, the anastomoses with the pulmonary arteries may be relatively close to the hilum, as well as in the periphery of the lung[11] Other systemic arterial collaterals, not strictly bronchial, enter through the mediastinal reflection, pulmonary ligaments and adhesions, when they exist, from such vessels as the internal mammary, pericardiophrenic, esophageal and intercostal Branches of the aorta may constitute the sole arterial supply in atresia of the pulmonary arteries, and this substitution by systemic vessels proceeds during ontogeny and may already be well developed at birth This is explained by the development of portions of the pulmonary artery in connection with the postbranchial arterial plexuses[12]

When a pulmonary artery in adult man becomes obstructed, as by embolism,

a collateral circulation develops, not from other pulmonary arteries, but by enlargement of the bronchials The mechanism of this expansion is probably somewhat as follows:[5] The onward flow of blood in the bronchial arteries, which normally terminate in the region of the respiratory bronchioles, is opposed by two forces, (1) the frictional resistance of the capillary wall and (2) the back pressure transmitted from the pulmonary arteries When the latter force is abrogated on occlusion of a pulmonary artery, more blood begins to enter through the bronchial vessels With increase in flow, there is an increase in the caliber of the vascular conduit by a mechanism not entirely clear, but one which has its counterpart during embryonic development Blood in the bronchial vessels may then reach the actual respiratory surface in the alveoli, whereupon gas exchange can take place In the absence of a high venous pressure, the lung does not usually suffer infarction When venous pressure is high, there is an additional counterforce which resists onward flow of oxygenated blood in the bronchial vessels Furthermore, the direct oxygenation of the walls of distal air passages from gases in the lumen is impaired by the thickening consequent to the increased venous pressure

*Experimental Studies of Arterial Collateral Circulation*

The quantitative evaluation of the volume of collateral blood flow is of interest, but this has been difficult to acquire in man, largely because, in chronic pulmonary disease, some of the collateral blood may be presumed to flow largely through tissue relatively remote from ventilated alveoli Newly developed indicator-dilution techniques should prove useful for measuring this component of the collateral circulation

A large collateral circulation can, however, be induced experimentally in the dog, as well as in many other species, by ligating a major pulmonary artery such as the main arterial supply of the left lung[13 17] The mechanism of this expansion has already been discussed in relation to pulmonary embolism, and is far beyond the requirements of "homeostasis" The minimal value of the blood flow can be estimated by bronchospirometry and appropriate analyses of blood gases[18] In the absence of infection, the pulmonary artery does not become thrombosed beyond the ligature, but comes into communication with vastly enlarged bronchial arteries by means of precapillary peripheral anastomoses[13] These may represent, in part, expansions of minute, probably previously capillary, connections That not all of the anastomoses are necessarily preformed is indicated by the fact that sprouts of newly formed vessels growing into the lung from the intercostal arteries by adhesions establish identical large connections with the pulmonary arteries just as they do in the chronically diseased lung of man The expansion of the vessels appears to be more rapid when ligature is performed in the newborn animal, suggesting the effect of hormonal factors,[19] some of which have been investigated[20]

Blood supplying the left lung from the aorta now has direct access to the capillary bed of the respiratory surface, which formerly was supplied by the pulmonary artery and where efficient gas exchange can take place[21] When desaturation of the systemic arterial blood perfusing these capillaries is pro-

duced by means of deep anesthesia under sodium pentobarbital (35 mg/kg), oxygen will be absorbed Flow in ml./min. can be calculated by employing a modification of Fick's formula

$$\text{Effective Bronchial Arterial Flow, E B F.} = \frac{a}{c\text{-}b}(100),$$

where a equals ml $O_2$ absorbed per minute when the left lung is supplied by pure oxygen through a bronchospirometric cannula, c, the oxygen content (in ml./100 ml ) of blood leaving the lung, and b, the oxygen content of blood entering the lung

Under the conditions of the experiment, b is the same as the oxygen content of systemic arterial blood, which is easily available; c is assumed to be the same as oxygen content of systemic arterial blood when both lungs are respiring oxygen, and this can be measured during a period immediately following the first part of the procedure It is most unlikely that c can be higher than this value, since it is evident from angiographic observations that a considerable part of the bronchial arterial blood perfuses the walls of the bronchi where it is inaccessible to direct oxygenation [22,23] Consequently, c-b is actually less, and the true bronchial arterial flow greater, than determined by the method just described.

By the use of this formula, the collateral blood flow in the left lung within two weeks after ligature of its main pulmonary artery has been found to be in excess of 100 ml /min , more than four times the maximum value established in the normal lung of the dog by Bruner and Schmidt, [24] it is a continuing increase, so that, at 18 months, the collateral flows approach 800 to 900 ml $/M^2$/min (fig 2)

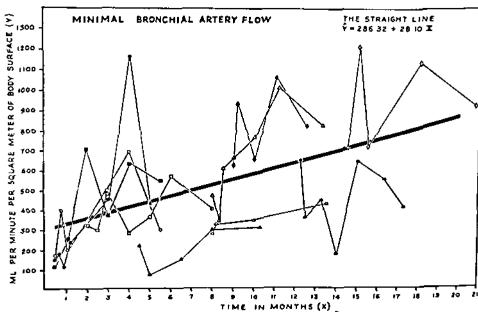


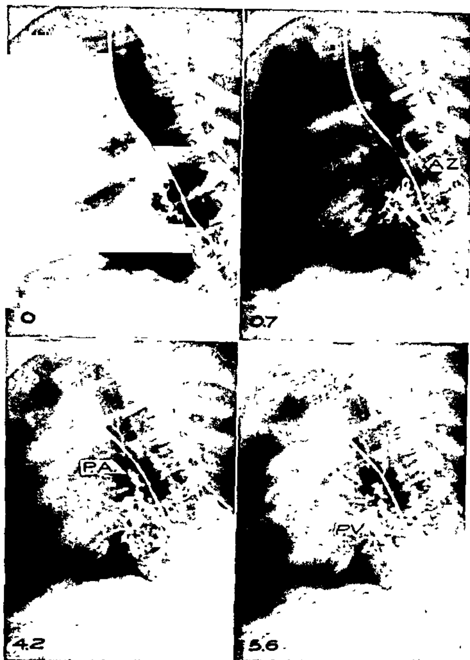

FIG 2 —Minimal bronchial arterial flow after ligation of the pulmonary artery Sixty observations in ten dogs plotted against time The heavy black line represents the statistical sum of the data Determinations on individual animals are connected The trend is significant statistically ($p < 0.01$).

It is possible to dissect the still patent blind end of the left pulmonary artery just distal to the ligature, and to measure the pressure within it. This tends to be slightly lower than the pressure in the main pulmonary artery, as would be expected from the lesser flow through a still largely intact capillary bed. When, however, the pulmonary veins that drain such a lung are occluded, there is a sharp rise in pressure to approach the mean systemic.[25] Normally, immediate obstruction of the left pulmonary artery and vein will induce only a slow and moderate rise in pressure within the latter.

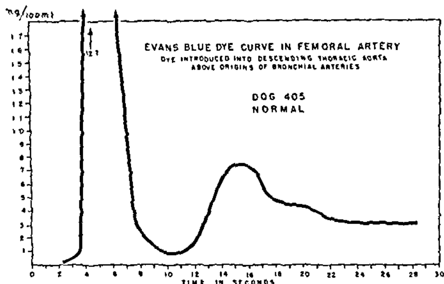
Hemodynamics: The methods of angiography and indicator dye distribution have been employed to investigate the hemodynamics of the newly developed collateral system.[23] When a contrast medium such as diodrast is injected by means of a catheter, introduced via a carotid artery, into the aorta just above the origins of the bronchial arteries, the latter become almost instantly opacified, usually within 0.7 seconds (figs. 3 and 4). Between 2.1 and 4.2 seconds after the injection of the contrast medium into the aorta, the left pulmonary artery becomes visible. Despite the fact of its previous interruption by ligature, which has made it, so to speak, a diverticulum with a blind proximal end, patency of distal left pulmonary artery is demonstrated in the living animal (fig. 5). Within 2.1 seconds, the left pulmonary veins begin to become opacified (fig. 6). This shows *in vivo* the passage of blood from the aorta by way of anastomoses with branches of the pulmonary artery beyond the ligature and thence through the pulmonary capillaries to the pulmonary veins. Aortography also indicates the very rapid passage of blood from the aorta through the intercostal vessels to the azygos vein (fig. 4), and this has been confirmed after intra-aortic injection of Evans blue dye, which reaches the right atrium within approximately two seconds.

The dye concentration curves, as obtained in the femoral artery, on injecting Evans blue into the aorta just above the origins of the bronchial artery, display a characteristic difference in animals with an extensive collateral, as compared with controls (figs. 7 and 8). That portion of dye that enters the collateral circulation pursues a circle that involves only the left side of the heart, and is, therefore, quickly returned to the aorta, as would be expected from the angiographic observations just mentioned. As a result, the curves for animals with a ligated pulmonary artery give evidence of early recirculation in a more rapid reversal of the first downward slope, and the dye in the distal aorta does not reach the low level of the controls before recirculation begins. Actually, the highest level before recirculation in the control group equals the lowest in the experimental. The observed values, usually in duplicate observations made 2 to 4 days apart, are indicated in table 1. (See page 86.) The second curve in the experimental group is complex and resembles in silhouette the bactrian camel, while the controls usually show only one major hump, like the dromedary (compare figs. 7 and 8).

The collateral circulation, representing as it does recirculation through the left side of the heart (fig. 9), is a burden entirely on that side. In the presence of the relatively intact low resistance pulmonary capillary bed, this burden is not large and, when investigated in rats, was found to be without effect on the size or weight of the cardiac chambers.[26] This may not be the case if the




FIGS 3 6—Angiographic series after introduction of contrast medium at the origins of the bronchial arteries in the aorta The bronchial arteries of the left lung are seen to fill instantly At 0 7 seconds the azygos vein, Az, is already becoming opacified The pulmonary artery (P A ) has been filled retrogradely by means of peripheral anastomoses with the bronchial arteries at 4 2 seconds (this process began at 2 1 seconds) At 5 6 seconds a pulmonary vein (P V ) is seen as a larger structure anteriorly of the pulmonary artery which is now beginning to fade The series demonstrates the passage of blood from the aorta to the bronchial arteries, thence to the pulmonary arteries and, by way of capillaries, to the pulmonary veins and back to the left heart.



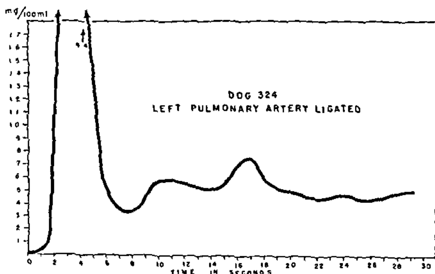




FIG 7.—(*top*) Evans' blue dye concentration curve after injecting the dye into the aorta above the origins of the bronchial arteries The concentration falls below 0 1 mg /100 ml before recirculation is indicated by initiation of the up trend The secondary curve is in the form of a prominent hump

FIG 8—(*bottom*) Curve analogous to that of figure 7 in an animal with left pulmonary artery ligated 11½ months previously Recirculation occurs before the downward slope of the first peak reaches 0 3 mg /100 ml, sooner than in the normal The secondary curves show two prominent peaks like a double humped camel, in contrast with the dromedary peak of figure 7 This is interpreted to represent several recirculations by way of the collateral channels and left heart

TABLE 1.—*Analysis of Dye Concentration Curves*

| Dog No | Time in Seconds: To first femoral artery peak | Recirculation start | Recirculation peak | Recirculation peak to equilibrium | Lowest femoral artery level before recirculation (mg %) |
|---|---|---|---|---|---|
| | **Left Pulmonary Artery Ligated (Plus Cardiopneumonopexy)** | | | | |
| 353 | 10 | 13 | 14 | 6 | 0 62 |
| 355 | 4 | 10 | 14 | 12 | 0 20 |
| | 4 | 13 | 15 | 11 | 0 29 |
| 320 | 4 | 9 | 15 | 9 | 0 28 |
| | 3 | 10 | 17 | 7 | 0 30 |
| 324 | 5 | 10 | 18 | 6 | 0 20 |
| | 4 | 8 | 17 | 5 | 0 33 |
| 321 | 3 | 10 | 14 | 5 | 0 30 |
| Mean | 4 6 | 10 4 | 15 2 | 7 6 | 0 32 |
| | **Control** | | | | |
| 401 | 6 0 | 13 | 17 | 11 | 0 15 |
| | 6 0 | 13 | 18 | 12 | 0.20 |
| 402 | 8 5 | 14 | 17 | 13 | 0 20 |
| | 6 0 | 13 | 18 | 9 | 0 15 |
| 403 | 9 0 | 22 | 27 | 3 | 0 15 |
| 284 | 4 5 | 10 | 14.5 | 14 | 0 00 |
| 405 | 3 0 | 9 | 12 | 16 | 0 05 |
| | 5 0 | 12 | 15 | 9 | 0 07 |
| Mean | 6 0 | 13.2 | 17 3 | 10 9 | 0 12 |

peripheral resistance is greater, as it may be in some diseased lungs In the same study, the left-to-left transpulmonary shunt was found not to produce an increase in blood volume. In this it is analogous to pulmonary arteriovenous fistula, rather than to systemic arteriovenous fistula

### *Significance of Bronchial-Pulmonary Anastomoses in Man*

The precapillary anastomoses that develop in organizing pulmonary disease have certain hemodynamic implications. There are two major differences from the experimental preparations just discussed First, the pulmonary arteries are patent proximal to the anastomosis (compare figs 9 and 10) Second, the capillary bed is destroyed by scarring to a variable degree

It may be expected that, where the high pressure systemic bronchial branches meet pulmonary arterial branches of approximately equal size, flow would be from bronchial to pulmonary arteries At the periphery of a spirally contorted and much branched arterial system such as the bronchial, however, there must be a large decrement from aortic pressure levels The actual pressure relationships at the points of anastomosis have not been measured and can only be inferred (1) There is evidence that pulmonary arterial blood is

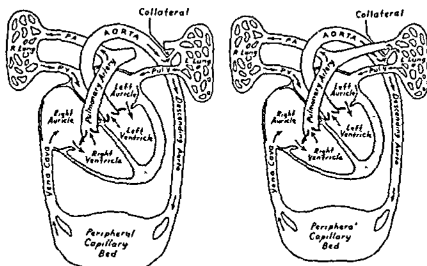



FIG 9.—(*left*) Diagram to represent circulation in an animal when the pulmonary artery of the left lung has been ligated. This lung now receives all of its arterial supply by means of expanded bronchial collateral vessels from the aorta. The blood is returned to the left heart by the pulmonary veins This presents a recirculation which is a burden entirely on the left side of the heart The output of the left ventricle exceeds the right by the volume of the collateral flow

FIG 10.—(*right*) Diagram of circulation in the presence of massive unilateral disease of the left lung where large anastomoses between the expanded bronchial and pulmonary arteries have developed, as in figure 1. That part of the blood that passes through the left from the collaterals is a burden on the left side of the heart The connections between the bronchial and pulmonary vessels, which are shown here in sum, represent points of resistance to the outflow of the right heart The possibility of recirculation towards the opposite lung against the direction of the stream in the left pulmonary artery is indicated by an arrow.

shunted away from the points of anastomosis in the diseased tissue to pulmonary substance capable of adequate gas exchange This is manifested by the usually normal or near normal oxygen saturation of systemic arterial blood, even when an entire lung is involved in bronchiectasis or tuberculosis[5] Although immobilization of the lung by parenchymal disease or pleural fibrosis contributes to this shunting, it has been observed that immobilization in itself is incompetent to prevent the entry of desaturated blood from the pulmonary arteries[27] (2) Anastomoses must then represent points of relative resistance to outflow from the right ventricle; when sufficiently large and numerous they would serve as one contributory factor among those that contrive to increase the burden of the right heart A volume of pulmonary substance exceeding that of one lung must be involved before this process becomes significant (3) In the presence of anastomoses, reversal of flow in the pulmonary artery is possible, and has been unequivocally demonstrated in patients with *total* bronchiectasis involving one lung The first patient,[5] a man of 32, studied in *1949*, had extensive bronchiectasis of all segments of the left lung. By angiography, all of the opacified blood in the first circulation was seen to go

to the relatively normal, but hyperexpanded right lung (figs. 11 and 12). Blood obtained by catheter just inside the patent left pulmonary artery was fully saturated, the catheter was not "wedged," and the blood came out under its own pressure. In another patient with similar disease, recently studied by Dr Ralph D Alley and associates of Albany, the observations on intravenous angiography were similar.[28] In addition, when contrast medium was introduced high into the aorta, as in the experimental dogs described, the bronchial arteries filled instantly as remarkably large vermiform vessels within the left lung Within two seconds, retrograde filling of the left pulmonary artery was demonstrated Thus, the passage of blood from the aorta to the bronchial arteries, and thence via anastomoses into the pulmonary arteries, against the normal direction of the stream, is demonstrated beyond peradventure in a living patient

That a similar reversal of flow can occur locally has been suggested by the observations of Roosenburg and Deenstra [29] Such studies, however, are immensely more difficult, and for technical reasons less reliable, than when there is total involvement of one lung Various possibilities are indicated theoretically in figures 13 and 14. With local involvement, reversal of flow can occur in a single branch The anastomosis has been pictured to be in a scar where much of the original capillary bed has been obliterated and where some newly formed vessels have been derived from the expanded bronchial arteries The resistance to blood flow here probably approaches that in systemic capillary beds, higher than in the pulmonary capillaries, and this favors reversal of flow locally As the main stream in the major pulmonary artery is joined, however, the reverse jet of oxygenated blood is swept into the low resistance intact peripheral capillary bed But, when the anastomoses are large and numerous, or universally present within the scarred parenchyma, reversal of flow in a major, or even into the main, pulmonary artery of a lung can take place, as demonstrated in the patients discussed in the preceding paragraph (figs 10 and 11) The direction of blood flow depends on the relative pressures in the pulmonary artery and bronchial artery, theoretically, at least, this might vary from one time to another.

## The Venous Side of the Collateral Circulation

### *Collateral Veins in Man*

The pulmonary and systemic veins are variably related in different individuals [1,30] Mediastinal veins, and even cardiac veins, may drain directly into the left atrium, presumably contributing some desaturated blood to this chamber, and thus to the systemic arterial stream Bronchial veins, which drain the first several orders of bronchi, in contrast with the relationship between bronchial and pulmonary arteries, communicate freely at one end with the pulmonary veins, and at the other they become continuous with the mediastinal plexuses that proceed to azygos system, and via the superior vena cava, to the right heart The blood flow in the true bronchial veins, at least as the azygos is approached, is towards that vessel, since that is the direction of the valves

Beyond their second order of branching the bronchi drain into the pulmonary venules directly. Venous branches from adjoining septa on all sides participate




FIG 11 —(*top*) Angiogram in a patient with bronchiectasis involving all segments of the lung The pulmonary arteries only of the normal right side are opacified, indicating a shunting of blood away from the diseased left A catheterization study revealed that, when the catheter tip was in the left main pulmonary artery, fully saturated blood was obtained, which had been flowing in reverse in that vessel, having arrived via anastomoses from the bronchial vessels The left pulmonary artery was patent at operation (fig. 12).

FIG 12 —(*bottom*) Segment of a cast from the resected lung of a patient whose angiogram is shown in figure 11 One of the large anastomoses between the bronchial, B A., and pul monary, P.A., is shown Direction of blood flow is indicated by arrows

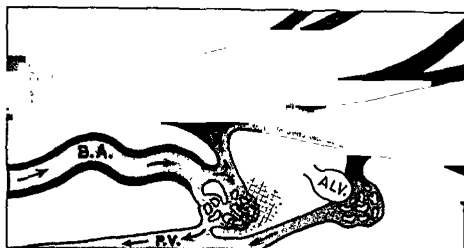






FIG. 13 —(*top*) Diagram indicating possibility of *local* reversal of flow in a branch of the pulmonary artery in the region of localized anastomosis associated with a small zone of scarring

FIG 14 —(*bottom*) Diagram indicating reversal of flow into a major pulmonary artery when multiple wide spread large anastomoses exist.

in this function and precapillary connections exist or are easily formed among them The pulmonary veins are, thus, not "end vessels" in the same sense as the pulmonary arteries

In advanced emphysema, and to a minor degree in more obviously fibrosing disease such as bronchiectasis, the bronchial veins expand remarkably (figs 15 and 16) and can be traced in continuity as definitely precapillary channels along the bronchi far into the periphery to the sixth order branches and sometimes beyond [30,31] With their expansion to exceed twice their previous caliber, the valves become incompetent, whereupon blood is free to flow in either direction With the development of *cor pulmonale* and right cardiac failure,



FIG 17.—Collateral venous system in a patient with bullous emphysema Posterior view of cast One of several enlarged bronchial veins, b.v., is seen to enter the azygos vein (Az). Peripherally, the former extend far out along the bronchi Their connections with the pulmonary vein are indicated in figure 16

the pressure in the right atrium and its tributary veins can come to exceed the pulmonary venous pressure which, under the circumstances, is not increased As a consequence, an extrapulmonary right-to-left shunt can develop, thereby contributing hypoxic and hypercapneic blood directly to the left heart The volume of this reverse shunt has not, as yet, been determined Introduction of an appropriate colored or radioactive indicator into the right atrium, with measurement of the dye curves in the pulmonary artery and aorta on the first circulation, may make this possible

Shunting of the blood into pulmonary veins has been demonstrated angiographically in chronic liver disease, another condition in which the azygos venous pressure can be increased [31] Cyanosis in patients with advanced hepatic fibrosis has been explained on this basis by Calabresi and Abelmann [32,33]

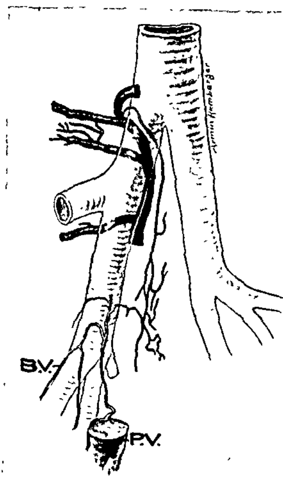



Fig 16 —Diagram of the circulation corresponding to figure 15, but from anterior view The expanded bronchial venous plexus (B V ) *is seen to be connected at one point with a large* pulmonary vein (P V.) which is shown transected The bronchial veins extend as injectable vessels to the periphery, far beyond the normal Proximally, the vessels proceed to the azygos The valves in the bronchial veins have become incompetent as indicated by their retrograde injection from the azygos Blood could, therefore, flow in either direction With right cardiac failure there could be a reversal of blood flow through these vessels, i e, from right to left, thereby contributing to the systemic arterial hypoxia and hypercapnia of advanced emphysema with *cor pulmonale* and right cardiac decompensation

### *Experimental Observations on the Venous Collateral Circulation*

When the pulmonary veins of an entire lung are ligated, a collateral circulation rapidly develops[34,35] Within five months it attains a minimal value ranging between 8 and 20 per cent of that expected, were the venous drainage intact The collateral veins are of two types (1) expanded bronchial veins of which the original connections with the pulmonary veins at the hilum are simply expanded and (2) transpleural veins which, after traversing adhesions, assume direct connections with the distal ends of the pulmonary veins These transpleural collaterals are obviously newly formed, since they have developed from capillaries within granulation tissue of the obliterated pleural

space. There is no concomitant expansion of arterial collaterals after this procedure, any more than ligature of the pulmonary arteries induces growth of venous collaterals.

If the animals are given penicillin and streptomycin postoperatively the lungs become intensely congested and edematous for several days, but do not become infarcted, as was invariably the case before these antibiotics became available[30 36,37] This indicates a contribution of infection to so-called "infarction" Within several months, the lungs assume a near normal gross and microscopic appearance, except for the expanded or newly formed collateral veins[38] The pulmonary veins usually do not suffer thrombosis

The collateral blood flow induces a transpulmonary right-to-right recirculation: the blood pursues the circle pulmonary artery, to capillaries, to bronchial and other systemic veins, to azygos vein, superior cava and right heart. Fully saturated blood can be obtained by catheter from the azygos vein under these circumstances

## The Lung After Experimental Interruption of Both Pulmonary Arteries and Veins

It is remarkable that the lung can survive ligature of both pulmonary arterial inflow and pulmonary venous drainage[39] Collaterals arrive from both sides, in a manner characteristic for each when it alone is stimulated to expand as described It is astonishing that the ingrowth of newly formed vessels arriving transpleurally is orderly, in that arterial collaterals invariably establish connections with pulmonary arteries, and the venous collaterals invariably come to drain pulmonary veins The forces that guide these vessels to their appropriate destinations are mysterious, but must be chemical, rather than purely mechanical If they were simply mechanical, then the larger than capillary connections should be in the direction of the greatest pressure drop, i e, from collateral systemic arteries to collateral systemic veins Such "short circuits" have, however, never been observed in the vinylite casts Instead, the course of the blood flow is apparently the most circuitous possible: from systemic collaterals directly, by precapillary anastomoses, to pulmonary arteries, to pulmonary capillaries, to pulmonary veins, and thence, by large anastomoses, to systemic collateral veins More than one influence must, therefore, be considered in the attempt to reply to John Hunter's still perplexing question, asked 200 years ago, "What makes vessels grow?"

It is also of interest that the rate of increase of the volume of collateral blood flow is not far different from that which occurs when the pulmonary artery alone is interrupted (fig 17) This suggests that the collateral veins can increase at least in proportion to the blood volume brought in by the expanding arterial collateral vessels The volumes of blood flow approach 60 ml /Kg./min at approximately 16 weeks following ligature of the vessels. This collateral circulation constitutes a left-to-right shunt across the lung

## Some Possible Applications of an Induced Collateral Circulation

The experimental observations that have been discussed indicate the possibility of redirecting blood flow within the thorax, with therapeutic intent

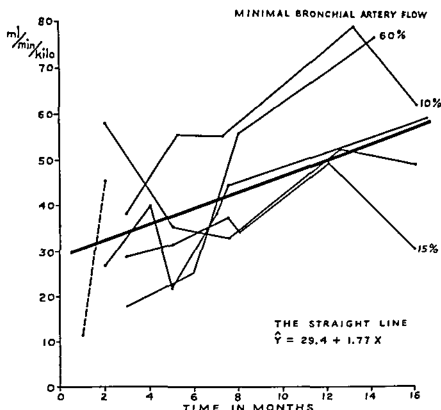



FIG 17 —Increase of collateral blood flow in ml/min/Kg after ligature of pulmonary artery and veins of left lung plotted against time The heavy black line indicates the trend calculated statistically which was found to be highly significant ($p < 0.001$) The percentages indicate the proportion of pulmonary substance of the left side, the draining vein of which had escaped ligature Data from one animal, for which only two observations are available, are not included in the calculation and the two points of observation are connected by a dashed line

## *Collateral Circulation of the Lung Applied to the Heart*

When the main pulmonary artery of a left lung is ligated and the lung is applied to the heart by pneumonopexy, several types of arterial bridges develop [22] (1) intercoronary connections of enlarged size, (2) transpleural connections between coronary and bronchial arteries and (3) retrocardiac connections of coronary with bronchial arteries The first mentioned is easily induced by a variety of simple procedures The last two, particularly the third, greatly exceed in size any arterial connections that have been induced by any other experimental procedure between the coronary vessels and an extracoronary blood source A new principle is employed to involve the coronary circulation in the development of collaterals to a neighboring organ and this is far different from simply causing two organs to adhere Although, when the coronary arteries are normal, the direction of blood flow is predominantly from the coronary to the pulmonary artéries, observations by dye distribution techniques have, nevertheless, demonstrated that, during a part of the cardiac cycle, some dye is transferred from the bronchial directly to the

coronary vessels by the large anastomoses which are established. This accounts for from 4 1 per cent to approximately 16 per cent of total inflow into the coronary sinus, even in the absence of myocardial ischemia [27] This method provides, for the first time, the means of measuring objectively a collateral circulation to the heart with chest intact The reversal of flow at different times in the cardiac cycle is probably the consequence of an out-of-phase relationship between pulse pressures arriving at the points of anastomosis directly along the coronary vessels from the sinuses of Valsalva on one hand and, on the other, through the more tortuous bronchial collateral vascular system (fig 18)




FIG 18 —Pressure pulse waves at a point of anastomosis between coronary and bronchial vessels induced by the effects of ligature of pulmonary arteries and cardiopneumonopexy are indicated diagrammatically as a dotted line (for the coronary pulse) and as a solid line (for pulse pressures transmitted through the tortuous bronchial vessels to the same point) It is evident that an out of phase relationship may exist during certain intervals of the cardiac cycle, when the pressure in the bronchial vessels exceeds that in the coronaries, although the latter are unobstructed During these phases, blood may flow from the bronchial to the coronary vessels via the precapillary connections to enter ultimately the coronary sinus, after traversing the same pathways peripherally that are pursued by blood arriving normally through the coronary arteries.

### *Redirection of Blood Flow in Transposition of the Great Vessels*

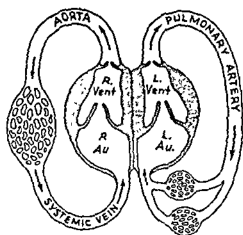
Double ligature of both pulmonary arteries and veins of the lung in transposition of the great vessels would have the effect of introducing an oxygenator, the lung, into the transposed systemic circuit [39] (figs 19 and 20) This redirection of blood flow would occur gradually and oxygenated blood thus introduced into the systemic circuit would tend to relieve anoxia Furthermore, the direction of flow of the oxygenated blood is inevitably in the desired direction, and is not unpredictable as when an interatrial defect is created in the attempt to treat this condition

## SUMMARY

The pulmonary vessels acquire collateral blood supply, not from each other, but from the bronchial arteries and veins Such a collateral circulation can be induced experimentally and occurs in pulmonary disease The two limbs of the collateral circulation develop independently of one another A lung can be maintained entirely on collateral inflow and drainage under experimental conditions

Within 18 months after experimental interruption of the pulmonary artery, collateral blood flow approaches 1 L /M $^2$/min Remarkably, comparable flows are observed after ligature of all arterial and venous vessels of a lung

In the diseased lung, expanded arterial collaterals coming into free anastomosis with the pulmonary arteries create a local increase in peripheral resist-



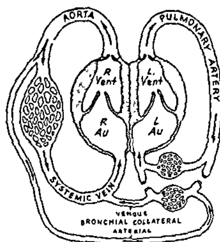




FIG 19 —(*left*) The circulation indicated diagrammatically in transposition of the great vessels There is no "crossing over" from right to left, except as determined by septal defects, or possibly by extracardiac connections between vessels of the two sides

FIG 20 —(*right*) Transposition of the great vessels indicated after ligature of the pulmonary artery and veins of one lung The latter then acquires its arterial supply from the bronchial arteries of the transposed aorta which, arising from the right side of the heart, contains desaturated blood. This blood is oxygenated in the lung and is then transferred to the right side of the heart by the collateral veins, thereby enriching the blood of the systemic ventricle This lung then acts as a built in oxygenator

ance, which directs blood flow from the diseased tissue into normal parenchyma: there may even be a reversal of flow into the pulmonary arteries from the bronchial arteries through the anastomoses.

Redirection of blood flow through collateral channels offers possibilities of application in therapy of coronary heart disease (cardiopneumonopexy after ligature of a major pulmonary artery), and in transposition of the great vessels (ligature of pulmonary arteries and veins to one lung)

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Note Figures 1, 3, 4, 5, 6, 15, 16, 17 and 20 have been previously published in the Am J Path and are reproduced with permission of the editor.

# Pulmonary Diseases: Structural Effect on the Pulmonary Vascular Tree

*By* DAVID M. SPAIN

ONLY THOSE STRUCTURAL ALTERATIONS in the pulmonary vascular bed produced by primary lung disease are of clinical and physiologic significance which alter the *perfusion of ventilated lung, increase the* pulmonary vascular resistance and enhance the enlargement or the development of various bronchopulmonary communications or shunts. The most consistent and prominent morphologic changes in the pulmonary vascular bed are actually secondary manifestations to the alterations in *blood flow, volume, and tension produced* by disease of the lungs. These changes consist basically of atherosclerosis in the larger elastic arteries, hypertrophy or at least apparent thickening of the muscular arteries and fibrosis of the intima in the smaller arteries and precapillary arterioles. Other secondary changes may at times also consist of autochthonous arterial thrombi and necrotizing arteritis or arteriolitis. These autochthonous thrombi may become so unrecognizable through organization as to be confused with arteriosclerosis. This has unfortunately led to the erroneous classification of some case as primary pulmonary hypertension. The necrotizing vascular lesions for years were misinterpreted as specific to rheumatic fever but more recently are regarded as the nonspecific effects of high pressure *in the pulmonary vascular circuit. These alterations in turn may then* contribute to the increased vascular resistance to the flow of blood.

In general the structural alterations of the pulmonary vascular bed of primary significance consequent to pulmonary diseases consist of varying degrees of obstruction, compression or obliteration of the capillary bed in ventilated lung (not necessarily well ventilated), luminal narrowing, occlusion or distortion of the smaller muscular pulmonary arteries, precapillary arterioles and veins, and changes in the immediate tissue environment of the vessels that tend to diminish their distensibility and alter transmural pressure.

There are several characteristics of the pulmonary vascular bed that serve to distinguish it from the systemic vascular bed and also influence the significance of the previously mentioned anatomic alterations. These are its distensibility potential, large reserve and relative lack of musculature. These low pressure factors are of importance in the proper evaluation of the relative importance of the effects of structural alterations in the pulmonary vascular bed.

Those primary lung diseases that effect the pulmonary vascular bed are numerous. A study reported over ten years ago on 100 consecutive autopsied cases of cor pulmonale revealed the following incidence of underlying "primary" *pulmonary disease (table 1). A more recent* study of consecutively

*TABLE 1.—Basic Underlying Pulmonary Conditions in 100 Consecutive Necropsies on Cases with Cor Pulmonale*

| Underlying pulmonary condition | Number of Cases |
|---|---|
| Emphysema (diffuse obstructive) | 51 |
| Bronchiectasis—diffuse, bilateral | 9 |
| Bronchial asthma | 6 |
| Silicosis and silicotuberculosis | 6 |
| Tuberculosis | 6 |
| Kyphoscoliosis | 1 |
| Thoracoplasty and tuberculosis | 5 |
| Primary pulmonary arteriolosclerosis | 1 |
| Diffuse interstitial fibrosis | 5 |
| Schistosomiasis | 1 |
| Foreign body emboli (morphine addiction) | 1 |
| Multiple pulmonary emboli with organization | 2 |
| Pulmonary artery thrombosis | 2 |
| Scleroderma | 1 |
| Boeck's sarcoid | 2 |

autopsied cases of cor pulmonale seen in the recent 10 year period reveals that idiopathic, obstructive or large lung emphysema has become both absolutely and relatively more important as a cause of cor pulmonale, whereas bronchiectasis, which is a disappearing disease, has decreased as an underlying pulmonary mechanism The significance of tuberculosis as a cause of cor pulmonale is difficult to evaluate since the types of cases vary from one institution to another Obviously in recent years the more chronic forms of tuberculosis are seen less frequently and consequently one does not see the long standing cases with fibrosis and secondary emphysema nearly as frequently. In past years the incidence of cor pulmonale in tuberculosis was related to the healing phase with emphysema as a consequence of repeated episodes of bronchogenically disseminated lesions There was no direct relationship between cor pulmonale and the degree of parenchymal destruction In certain areas of the country industrial dust exposures will undoubtedly be of greater importance Some investigators claim that there is an increase in diffuse interstitial inflammation and fibrosis of the lung In some of these cases cor pulmonale develops

In the pre-antibiotic era I had the opportunity of studying 200 consecutive autopsied cases of bronchiectasis that had not been treated with antibiotics or surgery In 38 of these the bronchiectasis was bilateral, diffuse and involved as well the smaller ramifications of the bronchial tree Twenty-five of the 38 had hypertrophy of the right ventricle In none of the other cases was cor pulmonale noted This would indicate that pulmonary disease generally must be widespread in order to produce significant structural alterations in the pulmonary vascular bed that will eventuate in cor pulmonale

In the 25 cases, it is important to note that emphysema was a prominent secondary feature. Liebow has demonstrated enormous broncho-pulmonary arterial communications in advanced bronchiectasis These shunts which allow

a high pressure system to communicate with a low pressure system cannot however be of prime importance in the development of pulmonary hypertension because cor pulmonale does not occur in bronchiectasis (as stated previously) unless the disease is diffuse, bilateral and accompanied by emphysema

Notably absent from the list of pulmonary conditions that cause cor pulmonale are those which produce cornification or organization of varying portions of the parenchyma of the lung (organized pneumonia, radiation pneumonitis with fibrosis and lipoid pneumonia) Although structural alterations of the pulmonary vascular bed in such areas are profound, the fact that there is no parenchymal function (ventilation) present renders these changes of little clinical or physiological significance The granulation tissue in these areas is supplied by the bronchial arterial system Only in those cases where the anatomic extent of lung involvement is so great as to deplete the vast reserve of the pulmonary vascular bed, does one see any clinical or abnormal physiological manifestations

The most important and basic underlying pulmonary disease that compromises the pulmonary circulation is emphysema This includes the so-called primary idiopathic or large lung type, the pathogenesis of which is still in dispute, as well as the forms of obstructive emphysema that are secondary to other primary pulmonary diseases such as bronchial asthma and silicosis Anatomically, it is difficult, if not in most instances impossible, to definitively recognize emphysema unless it has entered the destructive phase wherein the alveolar walls are disrupted with coalescence of the alveolar spaces This alteration of the alveolar walls is the key to the morphologic alterations in the pulmonary vascular bed in emphysema The alveolar walls are destroyed, thinned, disrupted, or at times thickened with fibrous tissue, inflammatory exudate or an increase in smooth muscle These alterations affect the capillary bed directly, as well as some of the larger vessels (veins and arteries) Difficulties in quantitative measurements of the changes in the capillary bed are numerous The techniques that are often so advantageously applied to the study of the larger vessels and bronchopulmonary communications require injection pressures sufficiently high so as to make them unrealistic for the study of the capillary bed Furthermore, it is difficult to simulate the intra-alveolar pressure relationships that exist during life However, some information can be gained from a poor substitute, and that is the study of hyperemic or congested emphysematous lungs at post mortem in the human It should be remembered that to study sections of the lung in this way relative to pressure, flow and ventilatory inter-relationships in analogous to studying one flat still film in a three dimensional motion picture, and yet despite the errors and limitations inherent in such a study it is often possible to demonstrate certain alterations and relationships

In comparison with the congested "normal" lung there is a diminution in the number of hyperemic capillaries in many areas of the emphysematous alveolar walls In the "normal" lung the distribution of the congested capillaries is regular whereas in emphysema it is irregular A relatively larger number of precapillary arterioles and smaller arteries are seen in alveolar

walls Some of these thin-walled distended vessels may even be capillaries Thus many of the red blood cells passing through these vessels in the alveolar walls are now quite a distance from the alveolar capillary interface. In the normal lung the capillaries usually are only distended to the caliber of the diameter of one red blood cell Undoubtedly the fact that often terminal bronchiolar passages are included in the distended emphysematous spaces accounts for the incorporation of greater numbers of the larger vessels in the emphysematous space walls Many of the capillaries (distended or not) are removed from intimate contact with the alveolar interface by fibrous tissue, smooth muscle or inflammatory exudate To make the situation more complex fairly well perfused alveolar walls may exist in areas where, from a structural point of view, there would appear to be inadequate ventilation In contrast, one may observe meager perfusion in alveoli that would appear to have been better ventilated This is partly the consequence of the varied interplay of mechanical alterations that on one hand distends portions of lung and on the other hand may partially compress adjacent pulmonary parenchyma There is also elongation, distortion and compression of the larger vessels (veins and arteries) that course through the emphysematous areas These in turn may be supplying or draining capillaries in areas of pulmonary parenchyma that are relatively normal The variety of these changes is great from one portion of the lung to another and exists even in the smaller pulmonary sub units In fact variation and lack of homogeneity is the characteristic pattern This condition of varied alveolar wall-capillary imbalance is perhaps one of the *basic consequences of the structural alterations that occur in emphysema* The implications of this relative to proper interpretation and evaluation of various function tests are quite obvious (fig 1)

In addition to the direct anatomic alterations on the capillary, arteriolar, small arterial and venous bed, the indirect effects of the altered pressure relationships that occur in the environment of these vessels as a consequence of emphysema, may perhaps be of even more importance In emphysema, as well as in other pulmonary conditions, profound effects on function (hypoxia etc ) alter the pulmonary blood flow, volume and tension in advance of the destructive effects of the disease on the morphology of the vascular bed

The relative importance of the direct structural versus the indirect functional effects on the pulmonary circulation may be illustrated by such conditions as kyphoscoliosis, complete unilateral thoracoplasty and the obesity syndrome In these conditions, in time, pulmonary hypertension develops which may be severe enough to produce cor pulmonale, yet in some cases of kyphoscoliosis as well as unilateral thoracoplasty the emphysema and the structural changes in the blood vessels are entirely inadequate to account for the cor pulmonale In the obesity syndrome, of course, there is no emphysema or notable primary structural alterations in the pulmonary vesicular bed Situations of this sort indicate that such factors as hypoxia and hypervolemia are perhaps the primary factors in the development of pulmonary hypertension rather than the structural alterations that develop later, in the destructive and irreversible phase of pulmonary disease processes *In kyphoscoliosis and unilateral thoraco-*



FIG 1 —Emphysema of lung showing varied picture of alveolar distention and disruption

plasty, unilateral kinking of vessels is probably not a factor because the secondary vascular manifestations of pulmonary hypertension are equally reflected in both lungs

In an entirely different area of lung disease one may observe that in the broad group of conditions in which the inflammatory and fibrotic process is interstitial, cor pulmonale also occurs In this group which includes the non

specific interstitial fibroses, beryllosis and sarcoid, the blood vessels throughout the lung are encased *in an environment of fibrosis, inflammation, granulation* tissue and edema This undoubtedly reduces the distensibility of the entire vascular bed. The alveolar-capillary block and diminished ventilation of the lung in these conditions contributes important functional disturbances that hasten the onset of pulmonary hypertension.

Direct structural involvement of the pulmonary arterial *system* with thrombi, embolic carcinoma, polyarteritis and schistosomiasis requires no comment as to the obvious increase in the resistance to the flow of blood that occurs in these conditions Plexiform vascular arrangements have been observed in these conditions similar to those noted in the pulmonary hypertension in congenital cardiovascular disease Whether these plexiform vascular arrangements are by-passes, vascularized granulation tissue or shunts is not always entirely clear

In summary, then, the structural affects on the vascular bed in the distribution of emphysema produces a varied picture of profound alveolar wall-capillary imbalance.

Distinction must be made between those structural alterations in the pulmonary vascular bed produced by lung disease that are primary to the development of pulmonary hypertension and those that are secondary Close correlations are not always apparent between the extent of morphologic vascular change and the degree of cor pulmonale Observations on a variety of pulmonary diseases indicate that functional factors are perhaps of greater significance than anatomic alterations in the earlier stages of pulmonary hypertension in acquired pulmonary disease

## Discussion

Liebow Similar observations were made some years ago by Drs Alley, Shedd and Lindskog in which the pulmonary artery of one side having been ligated some months before, the pulmonary veins of the same lung were occluded In contrast with the normal, there was a much sharper rise in pulmonary venous pressure

In this case, of course, the pulmonary vein is, so to speak, a sac with a closed end, but open to the bronchial arterial side from which pressure is transmitted to it, and drained in small part by connections with small bronchial veins.

*Forster One of the problems that has always interested* us is the state of the pulmonary capillary bed in emphysema. This question can be directed mainly to Dr Spain I believe that most people feel the main difficulty is not in loss of diffusing surface in the capillary bed (at least in the milder stages of physiological impairment) but in the unevenness of distribution of blood and gas, and therefore, we are always looking for some hole or weak spot in the classical idea that emphysema is destruction of the capillary bed, and I wondered if Dr Spain would comment on that Also I have seen some articles that suggest that the broken capillary walls are perhaps an artefact, depend-

ing on how much distention of the lungs there is when they are sliced. Would you comment on this and other possible artefacts?

SPAIN: As far as the question of artefact is concerned, I think one just has to look at some of these lungs before they have been touched at the autopsy table in order to realize that the alveolar walls are destroyed. This is before being cut or processed so that the question of artefact does not enter into it. In the nondestructive phases of emphysema the problem is more difficult and one can never be sure. How much the alveolar destructive obliteration of the capillary bed contributes to the total picture is difficult to estimate because of the tremendous vascular reserve. I think what is more important, however, is the lack of balance that exists in ventilated areas with varied and irregular distribution of capillaries, and in other areas that are poorly ventilated in which the perfusion at least on an anatomical basis appears relatively unimpaired. There are also vessels that course through relatively well ventilated areas to less ventilated areas, and then there are vessels that course through regions where the pressure exerted on them may be abnormal, but then may eventually supply better ventilated alveoli. To compound the problem, uninvolved lung may be compressed by adjacent emphysematous spaces. How one is able to apply a formula to these variables is almost beyond comprehension.

Originally, years ago I was impressed with the fact that the all-important disturbance was ventilatory and not in the diffusion, but as one studies the situation, one is struck with the fact that there must be a serious inescapable diffusion disturbance.

Dr. Naeye at Columbia University is getting around this problem by measuring the intimal thickness, the medial thickness and the lumen diameter, and then has worked out a ratio in order to try to correct for the contraction factor which undoubtedly exists. With the use of this ratio there appears to be a definite increase in muscle beyond that accounted for on the basis of contraction.

COURNAND: The work of Dr. Liebow is undeniably admirable. We have been interested in the same problem, but in the living man. Drs. Fritts and Chidsey have made an attempt to estimate the effective bronchial flow, i.e., that fraction of the flow through the bronchial circulation returning to the pulmonary veins, by injecting a dye indicator substance near the right atrium and sampling simultaneously blood from the pulmonary and the brachial arteries. The dye dilution curve obtained in the former vessel measures the right ventricular output and in the latter the left ventricular output. In addition, a control measurement of cardiac output was obtained by the conventional Fick method.

Unfortunately, the spread of difference between the flow measurements in normal subjects by the two methods and at the two sites, pulmonary or brachial arteries, is of the order of ±15 per cent, although mean values are almost identical. If, in a group of patients, the average left ventricular output is significantly greater than the right, or if, in a patient, the left ventricular output is 15 per cent greater than the right, the chances are that the effective

bronchial flow is larger than usually observed In our experience, it is only in a group of cases with bronchiectasis that difference in flow between both ventricles becomes significant, however, it is also exceptional when the estimated effective bronchial flow reaches 1 liter or more. Such a large bronchial flow has been observed in a case with destroyed lung, very similar to the one demonstrated by Dr Liebow Interestingly enough, after resection of this destroyed lung, the difference between right and left ventricular output was no longer significant As a facetious parting shot, may I inquire whether in selecting a case for your demonstration of the importance of the development of bronchial circulation in the course of bronchiectasis, you have not done what the physiologists often do, that is, to exhibit only their best experiments or curves?

LIEBOW Following Forster's law of "best curves forward," the patients in whom actual reversal was clearly demonstrated were the only two otherwise suitable for study in whom all necessary observations could be made It is very difficult to come by patients who have massive unilateral disease where it is possible to catheterize both pulmonary arteries With lesser involvement, the technique necessary to demonstrate reversal is much more subject to error than when the entire lung is involved.

Even where the patients had massive unilateral disease, the pulmonary arterial pressure was not elevated despite the fact of reversal of flow in the left pulmonary artery that has been demonstrated Quantitatively, the anastomoses are important in raising pressure only with extremely widespread lesions involving more than the volume of one lung, or when added to other factors tending to displace pulmonary arterial pressure in the same direction.

CHAIRMAN EDWARDS In mitral stenosis are the bronchial veins enlarged?

LIEBOW In the cases we studied by injection techniques those veins which we consider true bronchial veins, namely those which go to the right side of the heart were not enlarged Others have observed markedly congested veins in the bronchi However, these are vessels which drain into the pulmonary veins

FERGUSON I would like to say something about vascular changes which occur with age. I think they are relevant to what Dr Spain was talking about

Many of the patients who undergo pulmonary resection are, of course, in the age group above 40 or 50 If the pulmonary artery pressure is measured before and after occluding one main branch, it almost invariably rises in older persons but does not do so in the younger people

One of the things which may be present is emphysema, as Dr Spain mentioned However, in some of these people there is no evidence of this Inspecting the vessels in their lungs one sees that they no longer have the structure found in the young adult There is a partial replacement of the muscle layer by collagenous fibers It would look, from the morphological point of view, as if they had lost their capacity to distend This is one of the limiting factors in pulmonary resection in older people

I wonder if Dr Edwards or Dr Spain would comment on some of these

changes? I don't think that they are necessarily disease changes Some of these patients we have operated upon for a nodule and there was no reason to suppose that the lesion itself would affect the pulmonary pressures.

CHAIRMAN EDWARDS: I wonder, Dr. Ferguson if you will say a word about the range of elevation in pressure under the circumstances that you mentioned, wherein the pulmonary vessels appear to be normal except for age changes and what pressure you get after a section of the lung?

FERGUSON We have to remember that these patients are under anesthesia and turned on one side. With the chest opened, pressures in the young person range between 15 and 20 The range of pressure that we have found in supposedly normal people over 50 years old is up to 35 mm.Hg This is after occluding one pulmonary artery The initial pressures may range up to 30

CHAIRMAN EDWARDS. Dr Heath has been interested in age changes in the pulmonary vessels Would you care to say a word about that subject, Doctor?

HEATH A cellular intimal fibrosis occurs as a normal age change in the pulmonary arteries and veins of most people over the age of about 20 years This was fully described by Brenner in *1935* This is a surprising finding but one which must be recognized by all embarking on a study of pulmonary vascular histology

I should like to confirm Dr Spain's remarks relating to the lack of hypertensive changes in the pulmonary arteries in most cases of emphysema. Some pathologists I know in England have been disappointed by this during their studies of lung diseases They might well be jealous of their fortunate colleagues who are engaged in the study of pulmonary vascular lesions in congenital heart disease and have so much to look at

In the last 2 years I have examined the lungs of 6 cases with cor pulmonale with pulmonary hypertension, proven at cardiac catheterization In some instances the pulmonary artery mean blood pressure exceeded 70 mm Hg However, in all 6 cases, hypertensive changes in the pulmonary arteries were absent or slight I think the reason for this is that the pulmonary hypertension in cor pulmonale is not sustained or of sufficient duration to cause severe vascular lesions

SARNOFF I wonder if I may address a general question to this panel. Would any of the panel pathologists care to indicate whether there is anatomic evidence of structures which suggest the possibility of increased lymphatic runoff in patients with chronically elevated pulmonary vascular pressures?

LIEBOW I can only comment on experimental work which, unfortunately, does not give a complete answer It has to do with producing, acutely, a supravalvular stenosis in the left atrium by means of a snare and collecting the lymph from the right lymphatic and thoracic ducts simultaneously Under these circumstances, the increase in lymph flow is very large in proportion to initial flow, but in terms of ml per minute, it is very small.

SARNOFF I was wondering about the appearance of the lymphatics in the chronically diseased patient

LIEBOW These are markedly increased in size in some cases of chronic pulmonary disease where the muscle also is increased The so-called "muscular

cirrhosis" of the lung is almost always accompanied by marked enlargement of lymphatics We have no idea what this means in terms of flow or function; it might mean nothing except a response to obstruction.

CHAIRMAN EDWARDS · In answer to Dr. Sarnoff's question, I have, on occasion, in infants with various types of congenital cardiac disease where the pulmonary venous obstruction was the essential feature, seen markedly dilated lymphatics If you try making a systematic study of those, you run into cases where you cannot find evidence of lymphatic dilatation Sometimes this is quite striking and then, at other times, it isn't evident at all. I don't understand it

WOOD I would like to ask a question, Mr. Chairman You described some pretty pictures of fetal pulmonary arteries involuting in 2 to 3 months after birth; then you showed us two ventricles, right and left, equal in thickness in the fetus, and finally you showed two adult ventricles How long does it take the right ventricle to involute? How much time lag is there between involution of the right ventricle and involution of the arteries?

CHAIRMAN EDWARDS I would say that in most instances, after 6 months, the normal relationship is accomplished and very frequently it is accomplished considerably earlier than that Two or 3 months is not an uncommon age to see the normal difference in thickness between the right and left ventricles Of course, I realize that this is contrary to what the electrocardiogram says, since with it the time of arrival of the postnatal state is usually later. I cannot explain the difference but the fact is that as a rule the heart itself seems to show the change earlier than the electrocardiogram does

DUBOIS Dr Spain, I think, the difficulty the physiologists had this morning, stems in part from the fact that physiologists make numerical measurements which are dealt with in the centimeter, gram, second system I would like to make a real plea for equivalent measurements on an anatomical basis

For instance, when we came to calculate numerical relationships in the vascular bed and lungs, we found that we had to go way back to Miller, who measured diameters and lengths of vessels in one-half of one dog lung sometime in the 1890's So, if we are to match up our physiological measurements of pressure and flow with the anatomical studies, I would like to put in a request for numerical measurements of lengths and diameters of vessels

CHAIRMAN EDWARDS The point is very well taken, and the very apparent technical difficulties in accomplishing the ideal will be brought out in some of the presentations to follow.

# Structural Alterations of Systemic Vessels in Response to Systemic Hypertension

*By* E. E. Muirhead and J. A. Stirman

Sclerosis of small arteries and arterioles represents the major vascular change in hypertension. Although similar changes are observed as an expression of aging, the extent and degree of the sclerosis is accentuated by the hypertensive state.[1] Despite considerable study given to the vascular changes of hypertension fundamental aspects of the sclerotic process in arterioles remain obscure and consequently controversial. For some time three major questions have emphasized this enigma. How specifically is the sclerotic process initiated? What ingredients contribute to the sclerosis and what is their source? To what extent may certain phases of the process be reversible?

Apparently from the beginning of appreciation of this vascular problem the first question above has evoked a consideration of the extent which hypertension per se contributes to the vascular lesions. The second question has often devolved into a consideration of arteriolar hyalin, its source, distribution and relationship to arterial intimal thickening. The third question may be considered to arouse again the matter of medial hypertrophy and its implications.

On this occasion we should like to consider certain aspects of these problems in light of experience with arterioles from hypertensive human subjects and the work with bilateral nephrectomy (renoprival hypertension).[2-14] Specifically we should like to consider first arteriolar hyalin and its possible relation to vascular smooth muscle and to connective tissue elements, and secondly changes in the wall to lumen ratio of arterioles under certain delineated phases of renoprival hypertension. At this time emphasis will be placed on the lowering of the wall to lumen ratio, the structural changes which appear to contribute to this change, the apparent reversibility of certain of these changes and the similarity between the canine lesions and those of the hypertensive state in man.

## Material and Methods

Vascular hyalin from arterioles in hypertension of man, arterioles and glomeruli of diabetic subjects and arterioles in renoprival hypertension of the dog has been studied by staining and histochemical methods previously described.[2,3,7,9,13,14] Autolyzed smooth muscle has also been similarly studied in the test tube and after its injection into the kidney via the renal artery.

The wall to lumen ratio of arterioles has been measured by a modification of the method used by Kernohan, Anderson and Keith.[15] Two perpendicular

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outside and inside diameters were measured with the use of a standardized microscale in the eyepiece. The corresponding diameters were averaged, $\frac{OD - ID}{2} = W$ and W/ID gives an expression of the dimension of the lumen represented by the wall thickness (OD = averaged outside diameters, ID averaged inside diameters, W = wall thickness)

The tissues were fixed in neutral formalin (10 per cent) and paraffin blocks were cut at 5 microns and stained with hematoxylin and eosin. Visceral arterioles cut squarely were measured Vessels with distinctly undulating internal elastic lamellae indicating prominent postmortem contraction were not measured Arterioles from the viscera were measured and particularly from the gastrointestinal tract, adrenals, urinary bladder, liver and heart.

Five hundred arterioles from 23 normal dogs which were sacrificed for other purposes served as controls The frequency distribution of the outside and inside diameters of these vessels is given in figure 1 In the presently considered material the wall to lumen fraction for the normal group was compared with that derived from three groups of bilaterally nephrectomized dogs

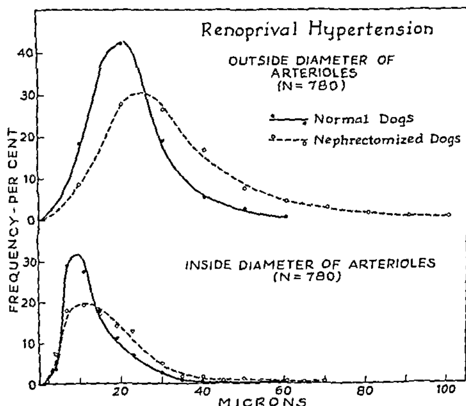



FIG 1.—The frequency distribution of the outside and inside diameters of arterioles from normal dogs (500 arterioles) and dogs with renoprival hypertension (780 arterioles) is depicted The nephrectomized dogs were sustained by peritoneal dialysis for an average of 38 and 41 days (20-111 days). During these intervals systemic hypertension was sustained The differences shown are significant

These were as follows I A group of 20 dogs which had been sustained by peritoneal dialysis for an average of 38 to 41 days (overall range 20 to 111 days),[16,17] II A group of 7 dogs which had been sustained by dialysis for 10 to 17 days,[18] III A group of 16 dogs which had been sustained by dialysis for 4 to 15 days and then had a homogenous renal transplant placed in the neck connected to the carotid artery and jugular vein This third group was subdivided into a group (IIIa) of 7 dogs which lived an average of 6 days beyond the transplant and a group (IIIb) of 9 dogs which lived an average of 16 days beyond the transplantation[19] The overall survival for group IIIa was 10 to 17 days and for group IIIb 20 to 32 days

In all groups a frequency distribution plot of wall-lumen ratio demonstrated a normal curve which was skewed to the left In order to apply statistical techniques to these data a logarithmic transformation of the wall-lumen ratio was used The derivation of a straight line when the log (wall-lumen ratio) $\times$ 10 is plotted against probability evidenced the transformation of a skewed curve to a normal curve.[20] Comparison of the different groups with each other and with normal was then accomplished by "t" test[21]

## Arteriolar Hyalin

We have proposed a distinction between two types of hyalin within sclerotic arterioles, that derived from connective tissue elements and that derived from the fusion of degenerated vascular smooth muscle[2,14]

The presence of connective tissue elements in the arteriolar wall as a feature of the sclerotic process has been attested to repeatedly Klemperer and Otani[22] interpreted the concentric deposits of cells and fibers or fibrils (onionskin change) of the arcuate and interlobular arteries in malignant nephrosclerosis as of connective tissue origin The intimal hyalin of benign arteriolarsclerosis may stain like collagen and contains cells resembling fibrocytes Moritz and Oldt[23] described this change and suggested an endothelial origin for the cells Moritz and Oldt also described collagenous deposits in the media

The vascular sclerosis of hypertensive nephrectomized dogs sustained for 10 to over 50 days contains connective tissue elements Hyalin deposits between the internal elastica and the endothelium contain cells, may stain metachromatically or may contain fibers or fibrils which stain as collagen Connective tissue elements may be observed in the media and here they may mingle with hyalin droplets and masses which resemble degenerated smooth muscle Concentric adventitial fibrosis may also be present The entire vascular wall may be transformed into a tube composed of concentric layers of connective tissue The increased cellularity of such a structure may be interpreted as a form of hyperplasia

The necrotic arteriole of malignant hypertension assumes the characteristics of "fibrinoid" Similar lesions are observed following bilateral nephrectomy of the dog particularly when a high intake of sodium and/or dietary protein are added to the management That fibrinoid of this type is derived mainly from disintegrated vascular smooth muscle has been supported by different observations

outside and inside diameters were measured with the use of a standardized microscale in the eyepiece The corresponding diameters were averaged, $\frac{OD - ID}{2} = W$ and W/ID gives an expression of the dimension of the lumen *represented by the wall thickness (OD = averaged outside diameters, ID* averaged inside diameters, W = wall thickness)

The tissues were fixed in neutral formalin (10 per cent) and paraffin blocks were cut at 5 microns and stained with hematoxylin and eosin Visceral arterioles cut squarely were measured Vessels with distinctly undulating internal elastic lamellae indicating prominent postmortem contraction were not measured Arterioles from the viscera were measured and particularly from *the gastrointestinal tract, adrenals, urinary bladder, liver and heart*

Five hundred arterioles from 23 normal dogs which were sacrificed for other purposes served as controls The frequency distribution of the outside and inside diameters of these vessels is given in figure 1. In the presently considered material the wall to lumen fraction for the normal group was compared with that derived from three groups of bilaterally nephrectomized dogs

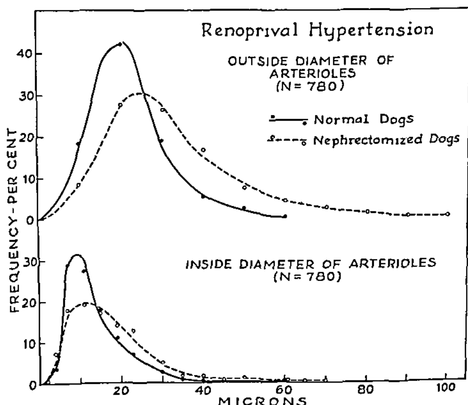



FIG 1—The frequency distribution of the outside and inside diameters of arterioles from normal dogs (500 arterioles) and dogs with renoprival hypertension (780 arterioles) is depicted The nephrectomized dogs were sustained by peritoneal dialysis for an average of 38 and 41 days (20 111 days). During these intervals systemic hypertension was sustained The differences shown are significant

*Wall to Lumen Ratio*

Expressed as the fraction of the lumen represented by the wall (W/L) this value is elevated as the wall of the arteriole thickens and the lumen either narrows, remains the same or is not correspondingly increased. In this study the wall/lumen fraction was elevated following nephrectomy. The thickening of the wall resulted from fibrohyaline thickening of the intima, myohyaline thickening of the media or the entire wall (fig. 2), fibrosis of the media and




FIG. 2.—(Verhof elastic stain, × 400 and × 340) A small artery and arteriole from hypertensive nephrectomized dogs (survived 40 days, mean arterial pressure 175 mm Hg). The vessel on the left displays intimal thickening due to the accumulation of cells and collagenous material (fibrohyalin). The vessel on the right shows acellular intimal hyalin with the characteristics of fibrohyalin and medial hyalin with the characteristics of myohyalin. The internal elastic lamina can be seen separating the two forms of hyalin. The wall is prominently thickened and the lumen is narrowed.

medial hypertrophy[6,7,8,9,13] Fibrosis of the adventitia occurred but was not considered in the measurements. The measurements indicated that the most common cause for the increased wall thickness appeared to be medial hypertrophy.

Hypertrophy of the media as considered in the discussion is similar to that

Transitions between vascular fibrinoid and vascular hyalin may be observed. Vascular hyalin may also develop within the smooth muscle fibers while pyknosis and karyorrhexis indicate serious injury of the fibers The staining, histochemical and spectroscopic properties of vascular fibrinoid and medial hyalin are quite similar.

Smooth muscle autolyzed in the test tube assumes the characteristics of vascular fibrinoid When this material is injected into the renal arteries it lodges in the kidney (arteries, glomeruli, tubules, peritubular areas) and here resembles fibrinoid early and vascular hyalin later.

The term "myohyalin" is being proposed for the vascular hyalin which appears to be derived from smooth muscle and the term "fibrohyalin" is being proposed for the hyalin apparently of connective tissue type These two forms of hyalin display markedly different staining and histochemical properties Their presence may be considered to imply a form of injury to the vascular wall somehow potentiated by the hypertensive state

## Measurement of Arterioles in Renoprival Hypertension

Use of the wall to lumen ratio [15, 23] in hypertension of man has yielded interesting and worthwhile information Applying this technic to kidneys in neurogenic hypertension of the dog Damin and co-workers [24] demonstrated thickening of the wall and narrowing of the lumen of arterioles. The foregoing contains information of this type in renoprival hypertension

### *Outside and Inside Diameter of Arterioles*

Figure 1 relates the frequency distribution of the outside and inside diameter of 500 arterioles from 23 normal dogs and 780 arterioles from 20 nephrectomized dogs which were dialyzed and maintained hypertensive for extended periods (20 to 111 days) The general contour and spread of the curves from the normal dogs are similar to those reported by Moritz and Oldt [23] for nonhypertensive man. In renoprival hypertension the outside diameter of arterioles increased and the increment was similar to that presented by Moritz and Oldt [23] for man and described by Kernohan, Anderson, and Keith [15]

The frequency distribution of the inside diameters indicated a tendency toward an increase of this measurement This difference was found to be statistically significant This finding differed from that of Mortiz and Oldt [23] who interpreted their data as indicating no change in the internal diameter of arterioles in hypertension Our data in this respect also depart from that of Kernohan, Anderson and Keith [15] who interpreted their material as indicating a narrowing of the lumen of arterioles in hypertension The overlap between normal and the renoprival data, however, is greater with data on the inside diameter than with that of the outside diameter

Part of the increment in inside diameter may be ascribed to the segmental stretching of necrotic and partly hyalinized vessels The relatively greater thickening of the wall following renal ablation elevates the wall to lumen fraction

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(table 1) indicating a prominent change in the wall to lumen ratio As discussed above the change resulted primarily from thickening of the wall.

TABLE 1 —*Statistical Analysis of W/L Data from Normal Dogs and Nephrectomized Dogs P Compares the Various Groups with the Normal Group.*

| Group | MEAN log (wall lumen ratio) × 10 | N | Standard Error | P Compared to normal |
|---|---|---|---|---|
| Normal | 0 6042 | 499 | 0 0094 | |
| Renal Transplant 10 17 *Days* | 0 5806 | 350 | 0 0200 | 0 5 |
| Renal Transplant over 20 Days | 0 8522 | 450 | 0 0102 | < 0 001 |
| Peritoneal Irrigation av 41 days | 0 8717 | 388 | 0 0151 | < 0 001 |
| Peritoneal Irrigation 10 17 Days | 0 8025 | 250 | 0 0189 | < 0 001 |

A comparison of changes in the wall to lumen ratio between the normal values and those of two groups of nephrectomized dogs which received homogenous renal transplants yielded interesting differences (table 1) A significant difference in the W/L fraction of arterioles was noted between the normal and nephrectomized dogs subjected to peritoneal dialysis for 10 to 17 days There was no difference in the arteriolar W/L of nephrectomized dogs which had a homogenous renal transplant up to the seventeenth day The arteriolar wall became thickened as indicated by the altered W/L when nephrectomized dogs with a renal homotransplant survived beyond 20 days It is to be recalled that a homogenous renal transplant in the dog begins to show significant degeneration after one week [19]

The comparison between normal arterioles and those of nephrectomized dogs surviving 10 to 17 days with and without a renal homotransplant (table 1) suggests protection against thickening of the arteriolar wall or reversion of the altered wall to lumen ratio under the influence of the renal transplants

Medial hypertrophy as described herein would be expected to be the most eligible arteriolar change for reversion under the influence of the transplant It is of interest that this change is the most common finding during this period in the absence of the transplant Medial and intimal hyalin would not be expected to revert readily

## Discussion

One may define arteriolarsclerosis as a structural alteration of arterioles which in its generalized form is initiated or potentiated by hypertension and which is characterized by thickening of the wall of the arteriole so that the wall to lumen ratio tends to be altered The thickening of the arteriolar wall may be mediated by an apparent enlargement of smooth muscle fibers of the

media (medial hypertrophy) with or without endothelial hyperplasia or by the accumulation of abnormal products within the vessel wall These abnormal products include connective tissue elements (immature or embryonal-like, collagenous or elastic) and a material with characteristics which are distinctly noncollagenous The latter material may be finely granular in the media or it may assume the properties of fibrinoid or hyalin and is usually present in the media and/or intima

Our experience has led us to speculations which have given rise to a unitarian hypothesis concerning the lesions of small arteries and arterioles in hypertension in man (mostly of "essential" type) and in experimental hypertension (for us mostly renoprival hypertension). In this hypothesis injury to the wall of small arteries and arterioles as a local or regional phenomenon is considered as the prime factor responsible for the ultimate changes observed We also prefer to consider the alterations of malignant and benign arteriolarsclerosis as related, and as concerned basically with changes involving constituents within the arteriolar wall

When the hypertensive state is accelerated or potentiated (malignant phase) the injury is considered to give rise to necrosis of the arteriolar wall The disintegrated products of the vessel wall, consisting mainly of disrupted smooth muscle, assume the characteristics of "vascular fibrinoid " The fibrinoid may spill into the lumen and is considered eligible to be swept along the blood stream and to embolize nearby capillaries This development may be particularly noteworthy with respect to glomeruli where the fibrinoid may well contribute to the alternative glomerulitis It is not difficult to visualize within *the framework of this hypothesis that when the injury is not so rapid and* fulminant in the malignant phase the media of the arteriole may not disrupt but give way in segmental foci As part of this injury one can visualize the deposition of an immature or embryonal-like connective tissue by the endothelium giving rise to the intimal thickening of the onionskin type As this accumulation occurs the media disappears through atrophy and disintegration

Medial hypertrophy of arterioles considered as an enlargement of intact muscle fibers may occur in the "malignant" as well as "benign" phase of hypertension It is not possible with the level of microscopy used thus far to determine whether this change represents a true increment in functional units within the muscle cell (true hypertrophy) or whether some other abnormality pertains, for instance, to the proposed "water logging" of Tobian and Redleaf [23] At any rate this change alters the wall lumen ratio while at the same time giving rise to the least apparent morphologic disturbance of the arteriole It is only fitting to entertain the possibility of reversibility of this lesion The data with renal transplants may represent reversion of this lesion under the influence of reconstituted renal tissue

More advanced lesions display a form of sclerosis which by its very nature implies ultimate fixation The two major ingredients result from forms of fibrosis (or elastosis) and hyalinization Our hypothesis leads us to consider the injury as more subtle and prolonged and associated with the repair process and a transformation of arteriolar smooth muscle into hyalin

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| Renal Transplant 10 17 Days | 0 5806 | 370 | 0 0200 | 0.5 |
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Hyperplasia of the media has been considered due to increased num
smooth muscle fibers by some workers but in general has connoted an inc
cellularity of the area

Collagenous and elastic connective tissue has been described in the
and collagenous connective tissue has been encountered in the media an
ventitia. Hyalin has been observed in the intima and/or media Its natu
remained obscure

2 The arteriolar lesions of renoprival hypertension of the dog are si
to those of hypertension in man Fibrinoid necrosis, medial hypertrophy,
lagenous thickening of the intima and media and hyalinization have
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altered in a manner comparable to that of hypertension in man The measu
ments indicate thickening of the arteriolar wall Two changes observed
human material have not been clear cut in the renoprival state. These
elastosis of the intima and the onionskin type of proliferation of the

3 Data have been obtained which suggest reversion of the wall to lum
ratio in renoprival hypertension by the influence of a renal homotranspla
It has been suggested that the reversion most likely pertains to medial hype
trophy

4 Observations have been related which are considered to indicate tw
types of hyalin in arteriosclerosis One type is considered to be derived from
connective tissue and occurs predominantly in the intima The other type
has been considered to represent mainly altered smooth muscle of the media
The terms *fibrohyalin* and *myohyalin* are being proposed for these structures
The hyalin considered derived from smooth muscle may be encountered in the
intima and/or media

5 The structural changes in arteriolarsclerosis are considered as due to local
or regional injury of arterioles mediated or aggravated by the hypersensitive
state It has been proposed that the magnitude of the injury may give rise to
necrosis, different types of fibrosis and hyalinization

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The fibrosis may be confined to the intima and here connective tissue hyalin may evolve At other times it traverses the vessel wall

A question arises concerning the confinement of fibrosis to the area of the intima in small arteries and some arterioles The possibility that the connective tissue is deposited under the influence of proliferating endothelial cells has been considered by several workers This interpretation is reasonable A basic point deals with the local mechanism stimulating the endothelium or other cells toward this change Could it be that segmental or focal decompensation of the vascular smooth muscle with a tendency to dilatation stimulates this intimal activity? This is a difficult possibility to put to experimental testing but is worth additional consideration

The hyalin of the media has been considered capable by us of a break through the internal elastica with either flow into the subendothelial zone or escape into the lumen with reincorporation down the vascular stream The experiments with autolyzed smooth muscle support these possibilities

The alteration of arteries and arterioles associated with systemic hypertension differs from those occurring in the pulmonary circuit in association with pulmonary hypertension Excluding the organization of occlusive masses, which is common in the pulmonary circuit,[26,27] other differences in the vascular lesions of the lesser and greater circulations during hypertension appear to be more of degree than of basic qualitative properties Thus intimal fibrosis (collagenous or elastic) is outstanding in pulmonary vascular sclerosis while the fibrinoid change and hyalinization are more prominent in systemic sclerosis

## Summary

1 A review of various descriptions and views concerning arteriolarsclerosis as observed in man has been considered The views as available in the literature on the morphologic changes of small arteries and arterioles as encountered in hypertension and also as an expression of aging may be summarized

a) In the "malignant or accelerated" phase two changes have been considered outstanding necrosis of the vessel wall which assumes the fibrinoid appearance, and hyperplasia of the intima consisting of cells, ground substance and fibrils The second change has been interpreted as consisting of an embryonal-like connective tissue in some vessels and definite collagenous tissue in others The endothelium has been suggested as the source of these cells As the intimal proliferation proceeds the media undergoes atrophy and/or necrosis. Medial hypertrophy has also been encountered in the malignant phase

b) In the "benign form" of hypertension the wall of the arteriole has been shown to be thickened while the lumen either remains in the normal range or is lowered Thus the wall to lumen ratio is lowered (the wall/lumen fraction is increased) The thickening of the wall has been interpreted as due to two basic changes, namely, hypertrophy or hyperplasia of the media and the accumulation of connective elements or hyalin in intima and/or media

The term hypertrophy of the media has been used for a general thickening in this area One type of medial thickening has been considered to consist of an increase in size of smooth muscle fibers Other types have been less distinct

MUIRHEAD: Dr Wakerlin, we would prefer to consider the main change of accelerated or malignant form of hypertension as involving disruption of the smooth muscle of the media so that the wall of the vessel assumes the characteristics of fibrinoid

We also prefer to consider the type of hyalinization in the benign form of hypertension which is noncollagenous and which is lipid containing and also contains other ingredients as a material which in essence is derived from alterations of the smooth muscle

Now, we believe that in experimental preparations, such as the nephrectomized preparation, transitions may be observed between the fibrinoid lesion and the hyalinized lesion We are not attempting to say by this approach that the two are not qualitatively different in so far as the general appearance is concerned, but what we are attempting to say is that our observations here would lead us to consider the basic source of material as the same, namely, an intrinsic change within the arteriolar wall involving the main ingredient there, smooth muscle

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## DISCUSSION

WAKERLIN Dr Muirhead, I wonder if you consider the arteriolar lesions of benign and of accelerated or malignant hypertensions as more or less of a continuum, or do you believe there is a qualitative difference between the arteriolar lesions of *benign and malignant hypertension? If so,* what is the nature of the qualitative difference?

eter, the intralobular artery. The retention of thick-walled, fetal-like pulmonary arteries when pulmonary hypertension has existed from birth is thus analogous to the retention of the fetal arrangement of elastic tissue in the elastic pulmonary artery subjected to similar conditions It can be seen, therefore, that like the right ventricle, the elastic and muscular pulmonary arteries and the pulmonary arterioles show hypertrophy in severe chronic pulmonary hypertension

With pulmonary hypertension the small muscular pulmonary arteries and pulmonary arterioles show progressive intimal proliferation which is at first cellular in nature, later fibrous, and finally fibroelastic with elastosis of the internal elastic membrane The intimal changes occur first in the pulmonary arterioles and the smallest muscular pulmonary arteries and progress until there is complete vascular occlusion Often a small endothelium-lined central channel remains The larger muscular pulmonary arteries rarely show intimal fibrosis

With the passage of time and the exaggeration of the elevation of pulmonary resistance by the occlusive intimal lesions, extensive dilatation of the pulmonary arteries and arterioles occurs with thinning of the media Fibrosis spreads from the intima into the media

At this stage in addition to the generalized dilatation, excessive localized distension of vessels occurs at the sites where the muscular pulmonary arteries give rise to arterioles, i e , proximally in the pulmonary vascular tree as side branches of medium-sized muscular pulmonary arteries and distally in the pulmonary vascular tree as terminations of small muscular pulmonary arteries These complex "dilatation lesions" are pathognomonic of severe chronic pulmonary arterial hypertension and may assume one of four main forms

## Dilatation Lesions

### *Arteriolar Veinlike Branches of Occluded Arteries*

The arteriolar branches of a hypertrophied muscular pulmonary artery may dilate proximal or distal to the site of fibrotic occlusion of the artery and form vessels that look like veins These characteristically cluster around the parent artery before passing to the lung substance to form alveolar capillaries

### *The Plexiform Lesion*

The branch may dilate excessively to form a sac, and plexiform masses of proliferated endothelium may form in this sac together with thrombus The cellular material in this plexiform lesion merges proximally with intimal fibrous tissue in the parent muscular pulmonary artery and eventually, itself, undergoes fibrosis

### *The Angiomatoid Lesion*

The dilated thin-walled branches may cluster in the lung substance to form an angiomatoid mass before giving rise to thin-walled vessels which eventually form capillaries in the alveolar walls

# Structural Alterations of Pulmonary Vessels in Response to Pulmonary Hypertension

*By* DONALD HEATH

IN THE PRESENCE of severe, chronic pulmonary arterial hypertension, characteristic histologic changes occur in the elastic and muscular arteries and the arterioles of the lung They occur in the media and the intima. In the fetus, the configuration of the elastic tissue in the media of the pulmonary trunk is similar to that of the aorta, although there are minor differences In both there are many elastic fibrils among the smooth muscle and collagen These fibrils are long, uniform, crenated and tightly packed and are parallel with one another Although this configuration of elastic tissue remains in the adult aorta, in the normal changes occur in the pulmonary artery so that the adult appearance is one of a loosely arranged network of branching, irregularly shaped, fragmented elastic fibrils A transitional pattern is found in infancy In severe pulmonary hypertension, the media of the elastic pulmonary artery thickens in all cases, but the configuration of the elastic tissue in it depends on the time of onset of the raised pulmonary blood pressure If the pulmonary hypertension is present from birth, as in cases of large ventricular septal defect or wide patent ductus arteriosus, the media of the pulmonary artery retains the fetal relationship to the aorta and has a similar elastic configuration to that of the aorta If the pulmonary hypertension develops in later life, as in atrial septal defect or mitral stenosis, the configuration of elastic tissue in the media of the pulmonary artery has undergone the transition into its adult pulmonary form In pulmonary hypertension, the intima of the elastic pulmonary arteries is the site of atheroma but not of severe intimal fibrosis

The muscular pulmonary arteries are vessels between 100 and 1000 microns in diameter The media of this class of vessel consists mainly of smooth muscle bound within internal and external elastic laminae, and the normal thickness of the media is 5 per cent or less of the external diameter of the artery In chronic pulmonary hypertension, this thickness increases to as much as 30 per cent of the external diameter While this increase is brought about mainly by the development of circularly arranged smooth muscle fibers, longitudinal muscle may develop, usually under the external elastic lamina Constriction may account for some of this increased medial thickness The normal pulmonary arteriole is 100 microns or less in diameter and consists of a single elastic lamina with an endothelial lining In pulmonary hypertension the arteriole has a thick muscular media like that of the fetal artery of comparable diam-

*This abstract is based on data derived from current research by the author and collaborators at the Mayo Clinic and Mayo Foundation which will appear in several papers*

This was interpreted as organization of a thrombus in the lumen of a pulmonary artery in which there was a contribution of vessels from a penetrating branch of a bronchial artery.

2 The second slide was of a cast of a lung from a patient with common ventricle who died at the age of 13 years Here the extreme tortuosity and rapid dwindling of small pulmonary arteries was demonstrated at which points there were connections with bronchial arteries interpreted to correspond with the observations of the preceding slide

HEATH I would not accept the 2 lesions that Professor Liebow showed as being angiomatoid lesions which are large discrete masses lying about 1 mm from the parent muscular pulmonary artery I would describe the vessels he showed as distended vein-like branches of muscular pulmonary arteries which are common in hypertensive pulmonary vascular disease Angiomatoid lesions are, in contrast, rare and I have in fact seen them in only 2 cases of large ventricular septal defect with pulmonary hypertension

LIEBOW: The first slide shown in the discussion represented a point where some of these vessels come into relation with the plexiform mass in the lumen At other levels, there was a true crown of additional vessels to form an "angiomatoid" lesion I am quite cognizant of the point that Dr Heath is making

CHAIRMAN EDWARDS Dr Heath, you might mention some of your work on the junction of the pulmonary and bronchial vessels in cases of high-grade pulmonary vascular disease

I wonder if you would care to comment about the possibility that some of these large vessels might possibly be bronchial collaterals.

HEATH: The bronchial arteries are enlarged in cases of hypertensive pulmonary vascular disease with widespread occlusion of pulmonary arteries These bronchial arteries are seen in the pleura, in the walls of the bronchi, and as enlarged vasa vasorum of the elastic arteries They give rise to thin-walled branches which enter the lung parenchyma

*The Cavernous Lesion*

The dilated branches may form cavernous spaces in the lung.

Occasionally the dilatation occurs, not in an arteriole, but in a small muscular pulmonary artery itself The media thins and there is intimal proliferation of fibrous tissue often in *an onion-layering pattern*

Each of these lesions is formed essentially from dilatation of arterioles or small muscular pulmonary arteries under the influence of chronic severe pulmonary hypertension Distended thin-walled sacs form which are seen throughout the lung These rupture and give rise to pulmonary hemosiderosis

Rarely, when the pulmonary arterial blood pressure rises to high levels, necrotizing arteritis occurs, and both acute and subacute phases of this process will be seen The arteritis appears to begin around the sites where both intimal proliferation and dilatation lesions first occur, i.e , at the junction of the muscular pulmonary artery and pulmonary arteriole The muscle undergoes necrosis, stimulates an inflammatory reaction, and is finally replaced by masses of granulation tissue in the intima, media, and adventitia

The early vascular changes which occur in atrial septal defect differ from those seen in ventricular septal defect in that cellular intimal proliferation in the pulmonary arteriole and smallest muscular pulmonary arteries precede the formation of a muscular media in the pulmonary arteriole In atrial septal defect too, in contrast to the state of affairs in ventricular septal defect, the normal transition to the thin-walled pulmonary arteriole occurs in infancy In atrial septal defect, medial hypertrophy and intimal proliferation are seen only with complicating pulmonary hypertension

## Discussion

LIEBOW The only comments I have are first, that it has been shown by Thomas and O'Neal and others that thrombosis is a very important factor when the walls of the pulmonary vessels have been damaged, and this certainly is a common occurrence in severe hypertension of the higher "Heath numbers "

The second point has to do with the angiomatoid lesions, the remarkable halo of vessels that Dr Heath has shown I wonder what evidence he has that these are in truth new sprouts, so to speak, of pre-existing pulmonary arteries If they are in fact such, it is the first instance where pulmonary arteries have been shown to act as collaterals for occluded pulmonary arteries

There is evidence in some patients who have had severe pulmonary hypertension, whether primary, or secondary to such conditions as common ventricle, that at least some of these channels are enlarged collateral vessels They are, however, stimulated only in those late stages where occlusion of the type that Dr. Heath demonstrated has occurred, thus, they are quite analogous to what happens when an artery is interrupted surgically

(At this time, two colored lantern slides were shown of material from extreme pulmonary hypertension where there were occlusive vascular lesions and angiomatoid changes) 1 The first showed penetration of a vessel through the wall of a pulmonary artery which was the seat of a plexiform occlusion

This was interpreted as organization of a thrombus in the lumen of a pulmonary artery in which there was a contribution of vessels from a penetrating branch of a bronchial artery

2 The second slide was of a cast of a lung from a patient with common ventricle who died at the age of 13 years. Here the extreme tortuosity and rapid dwindling of small pulmonary arteries was demonstrated at which points there were connections with bronchial arteries interpreted to correspond with the observations of the preceding slide

HEATH: I would not accept the 2 lesions that Professor Liebow showed as being angiomatoid lesions which are large discrete masses lying about 1 mm. from the parent muscular pulmonary artery I would describe the vessels he showed as distended vein-like branches of muscular pulmonary arteries which are common in hypertensive pulmonary vascular disease Angiomatoid lesions are, in contrast, rare and I have in fact seen them in only 2 cases of large ventricular septal defect with pulmonary hypertension

LIEBOW The first slide shown in the discussion represented a point where some of these vessels come into relation with the plexiform mass in the lumen At other levels, there was a true crown of additional vessels to form an "angiomatoid" lesion I am quite cognizant of the point that Dr Heath is making

CHAIRMAN EDWARDS: Dr Heath, you might mention some of your work on the junction of the pulmonary and bronchial vessels in cases of high-grade pulmonary vascular disease

I wonder if you would care to comment about the possibility that some of these large vessels might possibly be bronchial collaterals

HEATH: The bronchial arteries are enlarged in cases of hypertensive pulmonary vascular disease with widespread occlusion of pulmonary arteries These bronchial arteries are seen in the pleura, in the walls of the bronchi, and as enlarged vasa vasorum of the elastic arteries They give rise to thin-walled branches which enter the lung parenchyma.

*The Cavernous Lesion*

The dilated branches may form cavernous spaces in the lung Occasionally the dilatation occurs, not in an arteriole, but in a small muscular pulmonary artery itself The media thins and there is intimal proliferation of fibrous tissue often in an onion-layering pattern.

Each of these lesions is formed essentially from dilatation of arterioles or small muscular pulmonary arteries under the influence of chronic severe pulmonary hypertension Distended thin-walled sacs form which are seen throughout the lung These rupture and give rise to pulmonary hemosiderosis

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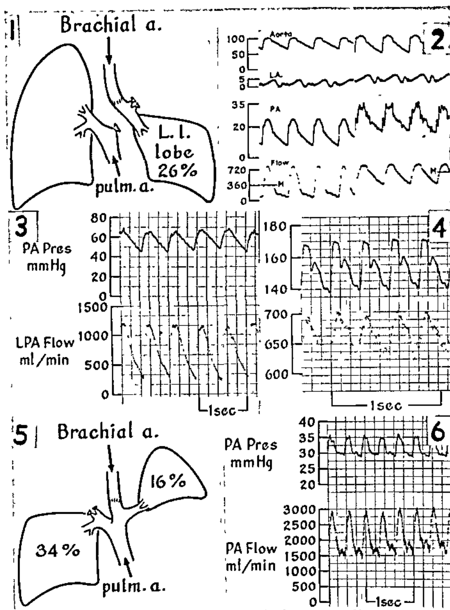



FIG 1 —Diagram of systemic artery shunt to left lower lobe

FIG 2 —Pressure and flow measurements before and after making type of shunt illustrated in fig 1

FIG 3 —Pressure and flow of shunt in a dog with mild arteriosclerosis, 8 months after operation as in fig 1

FIG 4 —As in fig 3, from a dog with severe arteriosclerosis

FIG 5 —Diagram of shunt into main pulmonary artery, with bilateral pulmonary resection

FIG 6 —Pressure and right pulmonary artery flow from a 10 Kg dog operated upon 5 years before as in fig 5 No arteriosclerosis was present

# Experimental Methods for the Production of Pulmonary Hypertension

*By* Donald J. Ferguson, Ernest M. Berkas, and Richard L. Varco

This paper is a review of experimental chronic pulmonary hypertension and pulmonary arteriosclerosis Recent unpublished data from our own laboratory are included where they supplement previously published work

Pulmonary hypertension occurs experimentally as a result of increased blood flow or from increased resistance to flow In either case, an augmented pulmonary blood volume may contribute to the higher pressure Increased flow per unit of lung follows pulmonary resection, or a shunt from the left heart into the pulmonary circulation Resistance to flow increases with narrowing of the pulmonary veins, or of the mitral orifice, and with the intravenous injection of emboli Somewhat more obscure are the mechanisms by which pulmonary hypertension and vascular changes developed in rats kept under 4 times the normal atmospheric pressure,[2] and in cats subjected to repeated convulsive doses of metrazol [15] Experiments with chronic hypertension, pursued beyond the mere inducing of vascular disease, have mainly involved use of a shunt or injection of emboli

## Shunt Method

### *Pressure and Flow Measurements*

The pulmonary artery in dogs may be anastomosed to the aorta,[16] brachiocephalic, or left brachial artery [6] (fig 1) If the pulmonary artery pressure, measured just proximal to the lung, is above 35 mm Hg when the shunt is first opened, fatal pulmonary edema is likely to occur then, or when the animal awakens from anesthesia and becomes active; if it is below 30, arteriosclerosis is unlikely to develop, even after several years With a shunt into only the smaller left upper lobe, the dog may survive pulmonary edema; sections show severe vascular trauma and hemorrhage [4] The mean velocity of blood in a brachial artery shunt to the left lower lobe is 60 to 70 cm /sec , and flow is turbulent (figs 1-6) Measurement of the lateral pressure in the shunt is difficult Left atrial pressure rises from 0 to 3 mm Hg when the shunt is opened (fig 2)

Flow has been measured either by the Fick method, allowing the dog to obtain oxygen only through the shunted lung, or with an electromagnetic flow meter [5] In the absence of arteriosclerosis, flow through a shunt to the left lower lobe, measured by the Fick method, approximates the normal resting cardiac output, thus doubling the output of the left ventricle [9] Circumstances are unphysiologic with this method of measurement, since arterial blood is desaturated. Shunt flow measured by the magnetic meter, with the chest open, averages initially 50 to 75 per cent of the resting right heart output, an in-




FIG 7—(Figs 7-10 are photomicrographs, Verhoff and Van Gieson stain) Pulmonary artery 80 μ in diameter showing medial hypertrophy, *from a dog* with shunt to left lower lobe

FIG 8—Recanalization of a 120 μ *pulmonary artery* observed 2 months *after shunt to* left lower lobe was removed and pulmonary artery was reanastomosed Large intima lined channels are present in the *media* and adventitia

FIG 9—Residual fibrotic plaque *in* 90 μ pulmonary *artery* 5 years after shunt which had produced severe arteriosclerosis was removed and pulmonary artery was reanastomosed

FIG 10—Fibrotic intimal thickening and focal atrophy of *media in* 200 μ pulmonary artery *(lower left)* 18 months after shunt which had produced severe *arteriosclerosis* was removed and pulmonary artery was reanastomosed The anastomosis was completely occluded The blood supply to the lung was through enlarged bronchial *arteries of* which several dilated branches are shown above, adjacent to the bronchus

of the other layers (fig 8) At 14 to 21 months the re-establishment of lumens is readily observed microscopically and resistance is doubtless lowered [7] Intimal cellular masses are replaced by relatively acellular fibrous tissue, which appears to have contracted, with enlargement of the lumen At five years the flow resistance was normal (under anesthesia) in one animal, in spite of many residual histologic abnormalities of the vessels (fig 9)

crease of 2 to 3 times normal flow to the lower lobe. As arteriosclerosis develops, shunt pressure gradually rises to the systemic level, and flow is reduced (figs 3 and 4) Under these circumstances, flow can no longer be conveniently measured by the Fick method Two animals with systemic shunt pressure and severe arteriosclerosis had blood flows to the left lower lobe, measured with the meter, equal to 25 and 30 per cent of the resting right heart output, or approximately the same amount of flow this lobe would carry under normal pulmonary artery pressure, in the absence of arteriosclerosis Resistance then was about 6 times normal

*Arteriosclerosis in Dogs with Shunt*

The media of arterial vessels from 20 to 100 microns in diameter of the external elastica may show thickening after two weeks of exposure to the shunt (fig 7) Intimal proliferation is noted at about 2 months and the most severe changes, with occlusion of many vessels, can be found after 6 months The adventitia shows an increase of collagenous fibers. There is no sudanophilic material in the arterial lesions, nor is any excess of polysaccharide substance, such as might result from dissolution of elastic tissue, found by the use of toluidine blue staining Thrombi are not an obvious feature of the process at any stage. Lesions are segmental in distribution, and are most prominent at the origins of branches, as is the case in human disease Veins, capillaries and the bronchial arteries remain normal in appearance (figs 7-10)

In our experience, about half the dogs that survive operation develop arteriosclerosis The others usually are found to have a narrowed or kinked anastomosis.

When the shunt is directed into the main pulmonary artery (fig 5), initial mean pressure and flow measurements are similar to those where the shunt is directly into the lung Vascular changes, however, are less frequent, milder, and later in occurrence After 20 to 80 weeks, 4 of 16 dogs with this type of shunt had slight medial hypertrophy of the pulmonary arterioles[9] The others had normal appearing lungs. One such animal with a resting flow 3 times normal per unit of lung and a mean pulmonary artery pressure under anesthesia varying between 26 and 32 mm Hg, has gone 5¼ years without developing any arteriosclerosis

A possible explanation of the different results with these two types of shunt is that the pulsatile thrust of blood in a direct shunt to the left lower lobe is transmitted to the small vessels, while in the other type this force is dissipated in the reservoir provided by the main pulmonary artery

*Regression of Arteriosclerosis with Pressure Restored to Normal*

Removal of a systemic-pulmonary artery shunt and re-establishment of the normal connections of the pulmonary artery restores pressure immediately to normal, although flow is doubtless reduced when arteriosclerosis is present Changes occurring in severe arteriosclerosis after this procedure have been studied in 4 dogs, in which the anastomosis remained patent, one of them now followed 5 years During the first 8 to 12 months, changes are slight, taking the form of capillary-sized recanalizations of the intima, and sometimes also

and intimal lesions in two, and also in two of the six controls. There have been 4 deaths from pulmonary hemorrhage in other animals of the experimental group Anticoagulants hardly seem likely to affect the development of medial hypertrophy, and thrombi identified histologically are seldom found at any stage in our experimental animals Nevertheless, minute depositions of fibrin or platelets may well play some part in intimal disease, and may be prevented by continuously effective anticoagulant therapy This problem requires more study.

### Venous Obstruction

It is necessary to narrow all the veins draining both lungs in order for pulmonary hypertension to develop [1,6] Excessive narrowing, for example enough to cause any rise of pulmonary artery pressure when the bands are applied, is likely to be followed by fatal pulmonary edema If constriction is much less, however, no hypertension develops later When the proper amount of narrowing is obtained, a mean pulmonary artery pressure of 20 to 30 mm Hg gradually develops Vascular changes are observed after 3 to 6 months, and resemble those seen with mitral disease The veins have increased thickness of adventitia and intima, and the arteries show slight medial hypertrophy with occasional intimal proliferation. Capillary basement membranes appear to be thickened, and there are macrophages containing hemosiderin in some of the alveoli.

Venous obstruction has been used in combination with a shunt,[6] in which case vascular changes are likely to develop rapidly, but the immediate mortality is high Experimental mitral stenosis in dogs can produce pulmonary lesions similar to those in human disease [13]

### Injection of Emboli

Harrison (*1948*) injected small emboli of human fibrin intravenously in rabbits, and found pulmonary arterial lesions which he thought were indistinguishable from those occurring in disease Others [11 12 14 17 18] used autogenous fibrin or clots, in both rabbits and dogs, and obtained similar vascular lesions when large and repeated doses were given Many emboli disappeared completely, apparently as a result of fibrinolysis Initially, sections of lung showed a cellular infiltrate and edema around the persisting emboli Capillaries were seen beginning to infiltrate the fibrin at 4 days, and new collagen was observed at 6 days The internal elastic was often fragmented Shrinkage or recanalization usually occurred, with the result that older fibrotic lesions were eccentric or polypoid No evidence of progression, fat infiltration or calcification was found in most of the experiments and pulmonary hypertension when measured was transient If injected rabbits were also given various natural fats or cholesterol, the number of embolic lesions was increased Cholesterol alone also induced pulmonary atherosclerosis, and this effect in turn was augmented by injection of fibrin emboli It is not known whether the presence of lipids increased the fibroblastic reaction to emboli, increased the coagulability of the blood, or interfered with fibrinolysis

If thrombosis of the reanastomosed pulmonary artery occurs, the vessels undergo changes similar to those found when it remains open, but in addition there are many enlarged, thin-walled branches of the bronchial artery (fig 10) Branches of the pulmonary artery distal to the obstruction contain oxygenated blood under low pressure

*Absence of Lipid*

In dogs with severe pulmonary arteriosclerosis, frozen sections of the lung show no sudanophile material We studied 7 shunt dogs in which blood cholesterol was artificially maintained at 5 to 10 times normal during the period of hypertension [3] Only a rare fleck of lipid appeared in the thick intimal lesions of the pulmonary vessels, while grossly visible atheromata developed in the coronary arteries and elsewhere The absence of lipid in sclerotic pulmonary vessels from dogs was also shown by microchemical analysis of sections of such vessels dissected out of frozen-dried lung These experimental data do not support a general hypothesis that atheromata are most likely to form where vessels are injured and the intima is thickened

*Effect of Lung Denervation*

Acute effects of pulmonary hypertension in dogs can be well studied with the preparations similar to that illustrated in figure 1 [8] The lung is perfused with fully oxygenated blood, so that hypoxic effects are avoided, and respiration of the part of the lung under study can be suspended or varied without changing the animal's condition

When an innervated lobe is first perfused by a shunt, the initial pressure often rises appreciably over a period of 5 to 10 minutes, and then slowly falls again Aortic and left atrial pressures do not change significantly during this period We surmise that the relatively high pulsatile pressure of the shunt, released suddenly into the pulmonary artery, has provoked a protective reflex contraction of the arterioles Such a process may occur repeatedly when the animal becomes active This pressure change is not observed in denervated lobes Muscular hypertrophy seen in the arterioles in early weeks of pulmonary hypertension implies that active contraction has been taking place

When the lung is denervated, it becomes more susceptible to pulmonary edema resulting from arterial hypertension This was shown in dogs prepared with a controlled shunt into a single segment of the left upper lobe Edema developed after denervation at the same or at a lower arterial pressure than that tolerated before denervation, while atrial pressure remained normal [8] Denervation has not prevented the development of arteriosclerosis in dogs with shunts These data suggest that the passive distensibility of the pulmonary arterial vessels in response to large increases of blood flow has an upper limit where active vasomotor regulation comes into effect, in part, at least, under nervous control

*Effect of Dicumerol*

We have followed 6 dogs with left lower lobe shunts and elevated prothrombin times for 6 to 12 months There have been definite arterial medial

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## DISCUSSION

DAMMANN Using a similar experimental approach we have produced changes comparable to those described by Dr Ferguson I would like to add if I might, one additional sequence of events, and offer a possible explanation If one creates a large left upper lobe pulmonary artery to subclavian anastomosis, a systemic pressure develops in the pulmonary artery distal to the shunt and the resultant vascular changes are those of an acute arteritis In serial microscopic studies, the first change to appear is hemorrhage in the area close to the anastomosis involving the vessel wall, perivascular space, and alveolar air spaces (fig 1) In the course of time, red cells are replaced by white cells



Fig 1—Section of lung showing a large branch of the pulmonary artery shortly after anastomosis with the subclavian artery

## CONCLUSIONS

1. Medial hypertrophy of the small arterial vessels is the first change to be seen in experimental pulmonary hypertension produced by a systemic-pulmonary artery shunt in dogs

2 *Proliferative intimal lesions causing high flow resistance can develop* within 3 to 6 months

3 An end-to-end systemic-pulmonary artery shunt is much more effective in producing vascular alterations than a shunt into the main pulmonary artery with a similar initial increase in mean pressure in the main pulmonary artery, and in blood flow per unit of lung

4 Accumulations of lipid are not found in pulmonary vascular lesions induced by a shunt, and high cholesterolemia does not affect such lesions in dogs

5 *When pulmonary hypertension is relieved, occlusive arteriosclerotic le*sions undergo a slow process of recanalization with a substantial reduction in flow resistance after 1 to 2 years

6 Narrowing of pulmonary veins or the mitral valve in dogs is followed by pulmonary changes similar to those in human mitral disease

7 Pulmonary edema can be induced by sufficient elevation of pulmonary arterial pressure, without change in the left atrial pressure After denervation of the lung, edema occurs at a lower arterial pressure Denervation of the *lung probably does not affect the incidence of arteriosclerosis in response to a* shunt

8 Dicumerol appears to have little effect on the development of experimental pulmonary arteriosclerosis

9 Intravenous injection of fibrin emboli may be followed by proliferative intimal lesions and, later, fibrotic plaques in the pulmonary arteries Feeding lipids increases the incidence of such lesions in rabbits.

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cular changes are accompanied by clearing of the alveolar spaces close to the anastomosis

I would suggest that the possible explanation for this progressive injury spread from a point close to the anastomosis out towards the periphery of the lung is that there is a time lag between fluid absorption from the alveoli and the intimal proliferation and medial hypertrophy of the proximal vessels Perivascular and alveolar hemorrhage at the acute injury site acts to increase extravascular pressure and acts as a barrier to prevent the spread of excessive flow and pressure to the periphery. As healing takes place and fluid is absorbed, the stress is transmitted on beyond the point of the initial damage Marked intimal proliferation occurs too late to prevent the injury spread

KATZ Mr Chairman, if I can go away from a purely pathological view to a more dynamic, the statement made by Dr Ferguson about pulmonary edema with denervation interests me and I would like to ask a question Depending on his answer I may or may not make a statement

CHAIRMAN EDWARDS I might interrupt by saying we consider pulmonary edema a pathological process

KATZ But the mechanism is physiologic The question is this Do you have any data in these experiments to show if there was a change in the vasomotor tone between the innervated and denervated lung to explain the pulmonary edema?

FERGUSON The answer is "no"

KATZ I have read your publication on this with great interest, and thought that maybe you had no such information, and so we have designed an experiment to test this

We have other experiments which I may have occasion to talk about in commenting on Dr Sarnoff's presentation, Saturday We have been interested in the mechanism of pulmonary edema, and so when we learned of your work we began making a preparation similar to yours in the dog, and we are measuring pressure gradients so that we can get an idea of vasomotor tone changes

If we find a change, then we will be satisfied because it will prove once again that the nerves do affect pulmonary vasomotor tone If there is no change, and edema develops, then we believe it might be supportive evidence to a concept we have expressed, namely, that the permeability of the pulmonary capillary wall can be changed in a neuro-humoral fashion to give rise to edema

DEXTER I wanted to ask two questions First of all are these lesions which you all have described this afternoon uniform and diffuse throughout the lungs or are they patchy?

The second question concerns thrombi I have seen thrombi in the pulmonary vasculature in various diseases which have been, and I am sure will be, discussed subsequently I am quite surprised that no one except Dr Liebow has even mentioned thrombosis I should like to ask what role thrombosis plays in pulmonary vascular disease And are you absolutely sure—I gather from your last discussion you are sure—one can differentiate the plexiform lesions from recanalized thrombi?

CHAIRMAN EDWARDS I can answer your first question to save time Pulmo-

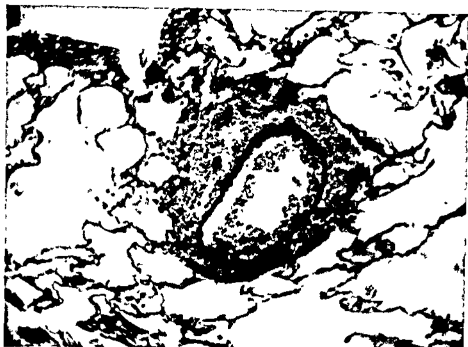


Fig 2 —A later section of pulmonary artery after anastomosis with the subclavian artery

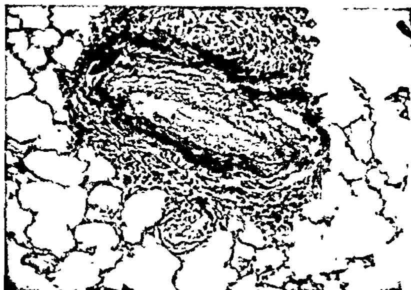


Fig 3 —A section of a more peripheral branch of the pulmonary artery after anastomosis of a large branch with the subclavian artery

and fibroblasts (fig 2) Medial hypertrophy develops in the involved vessels Distal to the acutely effected area there are dilated pulmonary arteries and a congested capillary bed. The next stage is a progression of the area of hemorrhage out towards the periphery, further medial hypertrophy and beginning intimal proliferation in the vessels injured earlier (fig 3) The vas-

However, the one point that I wanted to make is that as the hypertension remains for prolonged periods of time, this particular measurement is increased

HEATH · There appears to be formation of muscle in the walls of pulmonary arteries in severe, chronic pulmonary hypertension The elastic arteries for instance become thick-walled and dilated at the same time, a combination precluding constriction as a cause of the increase in thickness of the media. Longitudinal muscle is seen in these arteries as I illustrated in my paper Small muscular pulmonary arterioles, less than say 50 microns in external diameter, have too little muscle tissue in their walls to be explained by the constriction of normal muscular pulmonary arteries which usually exceed 100 microns in diameter

DAMMANN. In the experimental animal, following creation of a systemic-pulmonary artery shunt, one can find definite evidence of an increase in wall thickness The first change would appear to be dilatation This is followed by thickening of the wall Serial studies after the first dilatation demonstrate a steady increase in wall thickness without a change in lumen size Therefore, we must conclude that changes in wall thickness are not a result of dilatation, or constriction, but represent cellular hypertrophy

BAY Since I am neither a pathologist nor a surgeon, I feel entitled to ask Dr Dammann why those beautiful pictures of the hemorrhages between the media and the adventitia couldn't be regarded as surgically produced dissecting aneurysms

DAMMANN I think the spread of hemorrhage distally while healing occurs proximally is not the sequence of events one would expect from a surgically created dissecting aneurysm Furthermore, control biopsies taken before the anastomosis is fully opened fail to reveal perivascular hemorrhage

nary arterial lesions definitely are patchy Now, as far as the thrombi, Dr. *Heath or Dr. Ferguson*, which of you would like to start that discussion?

FERGUSON · I would say, as I said before, I haven't seen the thrombi at any stage in the lung, and the dogs go along for a long period of weeks or months without developing any change except medial hypertrophy I think this is the first change. We may see a small layer of intimal proliferation I don't know how one can say whether this began with a small amount of fibrin deposition or perhaps an accumulation of platelets on the vessel wall which technically, I suppose, would make it a thrombotic lesion. In any case, we don't see any gross thrombosis in any stage in the dog

DEXTER · You do see it, however, in the human diseases, don't you?

FERGUSON Yes

CHAIRMAN EDWARDS By studying patients at all stages you will observe some in whom lesions are just beginning The intimal lesions at first are cellular and later fibrous One does not see a group of cases with thrombi

There is one point that needs some clarification here and perhaps Dr Wartman may wish to comment on it If you inject clotted blood into the pulmonary vessels you may end up with fibrous lesions in the vessels Some of these lesions may simply be fibrous reactions proximal to the point of lodgement of emboli Dr Wartman, you have worked with this, would you care to make some comment?

WARTMAN First of all, I don't have any slides and I did not come prepared for this It is true that perhaps some of these might be lesions beyond the thrombi

I was also interested in what Dr Dammann said about hemorrhage around the blood vessels *If you inject particles into the blood vessels, these are sometimes* cleared out of the blood vessels and form little lesions similar to the ones he showed outside of the blood vessel. These seem to move further away as the hemorrhage clears

SHORT *I would like to raise a question about the use of the term hyper*trophy, because I think that the speakers have equated an increased wall-lumen ratio with hypertrophy

I would therefore like to ask each of the three speakers whether he has *actually measured the cross-sectional area of the media of comparable arteries*, whether systemic or pulmonary, and compared hypertensives with controls as O'Neal, Thomas, and Hartroft (*1955*) did in the case of mitral stenosis

MUIRHEAD Could you explain the technique a little better?

SHORT *I meant by taking the external diameter of the vessel and calculating* the area under the external circumference, then taking the internal diameter and defining this area, then subtracting one from the other and thereby getting a figure for the actual cross section of the area of media

MUIRHEAD. Well, the answer to the question would be "no" That approach has not been used at least in connection with our material as discussed here today.

Of course, we did measure the vessels from 23 normal dogs, each time making sure that the inner elastica did not appear to be unduly undulated

# The Pulmonary Blood Flow in Pulmonary Tuberculosis and the Effect of Unilateral Occlusion of the Pulmonary Artery

*By* B. Söderholm

THE PATHOPHYSIOLOGIC CHANGES that *may* affect the cardiopulmonary function in tuberculosis of the lungs are *manifold*. Both circulation *and* ventilation, and notably their interrelationships, are changed to a pathologic degree in a high proportion of patients with pulmonary tuberculosis. Since there is considerable variation from case to case, no generally valid picture can be given.

I shall outline here some of the results we have obtained in the investigation of a series, including patients with advanced and relatively slight lesions.

The reported incidences of right ventricular hypertrophy vary a good deal, but from autopsy series we have a figure of about 35 per cent for this condition, evaluated according to Muller (Samuelsson, *1952*). This figure is based on investigations conducted prior to the general use of chemotherapy. There is reason to expect a higher incidence *owing* to the longer survival time of cases with very advanced pulmonary lesions, because of our present therapeutic resources. Tending to corroborate this is a study reported by Bruce (*1951*), who found right ventricular hypertrophy *in* 75 per cent. Findings c[illegible]nicated by McClement and his associates (*1951*) also demonstrate a per- [illegible] despite roentgenologic regression of the [illegible] after clinical resolution of hematogenic [illegible]

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# IV. THE PULMONARY CIRCULATION IN PRIMARY LUNG DISEASE

CHAIRMAN: LARS WERKÖ

CO-CHAIRMAN: LOUIS N. KATZ

## Introduction

CHAIRMAN WERKÖ During the last 15 years physiologists and clinicians have studied the complex problems of the pulmonary hemodynamics in man in health and disease, at rest and under various forms of stress Much information has been gathered and many concepts earlier only surmised rest now on a firm ground In the field to be covered today there have been many new contributions to our knowledge, but there are more questions which have not yet been answered It is my hope that we will be able to correlate some of the data which have been gathered, and that in the discussion we may achieve a better understanding of what is going on in the pulmonary circuit in patients with lung disease

I would like to start out by placing a few provocative questions before you Is the cardiac output in patients with lung disease really increased? What regulates the cardiac output under these circumstances? Arterial unsaturation, hypervolemia or increased oxygen cost of breathing? Does the patient in failure have a high cardiac output? How should we define congestive heart failure in these patients and differentiate it from respiratory failure with hypoxia? Can we speak of a failing right ventricle when the work of the ventricle is increased several times over normal and over what the same ventricle does at another occasion, when no signs of failure are present? Is digitalis of any help to a patient when arterial unsaturation and hypervolemia seem to be the most important features of this situation?

Is the high pulmonary arterial pressure in lung disease due to hypervolemia, high cardiac output, anoxia or anatomical decrease of the pulmonary vascular bed? Or, rather, how much do each of these factors contribute to actual pulmonary hypertension in a given case? Can the pulmonary arterial pressure be influenced by drugs? If so, to what extent and by which mechanism? What happens during exercise?

# The Pulmonary Blood Flow in Pulmonary Tuberculosis and the Effect of Unilateral Occlusion of the Pulmonary Artery

*By* B. Soderholm

The pathophysiologic changes that may affect the cardiopulmonary function in tuberculosis of the lungs are manifold. Both circulation and ventilation, and notably their interrelationships, are changed to a pathologic degree in a high proportion of patients with pulmonary tuberculosis. Since there is considerable variation from case to case, no generally valid picture can be given.

I shall outline here some of the results we have obtained in the investigation of a series, including patients with advanced and relatively slight lesions.

The reported incidences of right ventricular hypertrophy vary a good deal, but from autopsy series we have a figure of about 35 per cent for this condition, evaluated according to Muller (Samuelsson, *1952*). This figure is based on investigations conducted prior to the general use of chemotherapy. There is reason to expect a higher incidence owing to the longer survival time of cases with very advanced pulmonary lesions, because of our present therapeutic resources. Tending to corroborate this is a study reported by Bruce (*1954*), who found right ventricular hypertrophy in 75 per cent. Findings communicated by McClement and his associates (*1951*) also demonstrate a permanent effect on the hemodynamics despite roentgenologic regression of the pulmonary lesions, for they found pulmonary hypertension after clinical resolution of hematogenic tuberculosis of the lungs.

This rise of pressure in the pulmonary artery may have several causes. In autopsy series, pleural complications and extensive fibrotic changes have usually been associated with right ventricular hypertrophy. It has also been observed that signs of cor pulmonale are more common in patients who have undergone thoracoplasty. These observations are consonant with the clinical experience that the roentgenologic extent of pulmonary lesions is not demonstrably correlated with the pulmonary arterial pressure. But on the other hand, several investigations have disclosed a positive correlation between pulmonary arterial pressure and respiratory insufficiency. Gaensler and his associates (*1955*) showed that in operations on patients with tuberculosis the mortality was much higher in those whose maximum breathing capacity was less than 50 per cent of normal. Uggla (*1957*), too, found that the maximum breathing capacity before operation was significantly higher in patients who were fit for work after operation than in cases that died or were disabled after operation.

In my own investigation, the pulmonary arterial pressure showed a nega-

tive correlation with the relative maximum breathing capacity (Soderholm, *1957*) The reduced maximum breathing capacity and elevated pulmonary arterial pressure may both result from the same etiologic factor—contraction of the lung tissue and the attendant reduction of the anatomic vascular bed—*and to alveolar hypoventilation accompanied by a functional reduction of the vascular bed* The latter factor is apparently of subordinate importance, as will be seen from figure 1

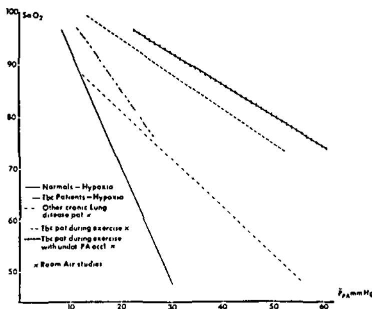



Fig 1 - Relationship between arterial oxygen saturation and pulmonary arterial pressure

Here we find that depression of the arterial oxygen saturation by induced hypoxia, produces in a tuberculous patient an elevation of the pulmonary arterial pressure of the same order of magnitude as that in a normal series This rise of pressure differs significantly from that observed in other cases of chronic pulmonary disease, and also from that associated with light exercise both with and without unilateral pulmonary artery occlusion An anatomic restriction of the vascular bed therefore seems most plausible, and evidence supporting this view will be given in the discussion on the effect of unilateral pulmonary artery occlusion

Another possible cause of pulmonary hypertension is an increased blood flow in the lesser circulation Available investigations show, however, a normal cardiac output both at rest and during exercise An elevated flow in the pulmonary circuit could be attributable to bronchopulmonary anastomoses, the occurrence of which has been established by the investigations of Liebow and his associates. Yet unilateral pulmonary artery occlusion in cases with widespread pulmonary lesions, in which this shunt might be expected, does not reveal any increased pressure peripheral to the occlusion Hence it is unlikely that etiologic significance attaches to an absolute increase of the flow.

The presence of pulmonary hypertension in catheterized cases cannot be taken to indicate the true incidence in a representative tuberculosis series, since these cases probably make up a selected group. It is worthy of note, nevertheless, that in the investigations hitherto reported the pulmonary arterial pressure, measured at rest, has seldom been appreciably elevated. In major series the mean pulmonary arterial pressure at rest averages between 15 and 20 mm.Hg If, on the other hand, the examination is also performed during light exercise, the incidence of pathologically elevated pressures rises to about 40 per cent (van Loo, *1955*) Here the upper limit of a normal pulmonary arterial pressure during light exercise has usually been set at 25 mm Hg

Investigation of the conditions during exercise is accordingly suitable for clinical purposes The physical working capacity, measured for instance by means of a bicycle ergometer, is appreciably reduced in pulmonary tuberculosis (Dahlstrom, *1957*) Here there is a negative correlation to the maximum breathing capacity The exercise, moreover, gives rise to arterial hypoxemia that is correlated to the rise of pulmonary arterial pressure (Soderholm, *1957*) Comparison of the rise of pressure during exercise with the subject recumbent, and the physical working capacity with the subject pedalling a bicycle ergometer, shows that the lowest physical working capacity occurs in cases with pulmonary hypertension In view of these relations it is likely that the restricting factor lies in the impaired breathing capacity, and that the effect on the hemodynamics of the lesser circulation is a phenomenon resulting from this ventilatory insufficiency The following case is illustrative

The patient was a 47 year old man whose tuberculosis had been detected in 1939, when he had moderately extensive lesions in the right lung and at the left apex He was treated with right artificial pneumothorax Left pleurisy supervened in 1952, and there was conspicuous bilateral progression in 1954 At preoperative examination, the patient had normal pulmonary artery pressure and normal arterial oxygen saturation, but even under light exercise the pressure rose to suspected pathologic values coincident with a fall in the arterial oxygen saturation The examination was therefore implemented by left pulmonary artery occlusion, which resulted in a marked rise of pressure both at rest and under the same light exercise as before In each instance the rise in pressure was accompanied by reduced oxygen saturation in the brachial artery These findings suggested that the patient would be unable to tolerate a major resection, but a smaller resection comprising 4 segments did not seem to be contraindicated, and was indeed performed without complications When followed-up 7 months after operation, the patient had normal pulmonary arterial pressures and oxygen saturation However, even during very light exercise the pressure rose to still higher values than the corresponding ones before operation, and when the exercise load was increased it mounted to excessively high values The arterial oxygen saturation at the same time fell commensurately The cardiac output was in the normal range both before and after operation At follow-up, however, the arterio-venous oxygen difference was already elevated at rest, and the patient was regarded as a case of cor pulmonale

In order to estimate the significance of a reduction of the anatomic vascular bed, we employed the technique of unilateral pulmonary artery occlusion described by Carlens, Hanson and Nordenstrom (*1951*) With this method a double-lumen catheter is advanced to the desired position in a pulmonary artery, whereupon the balloon is filled with contrast medium This makes it possible

to localize the tip exactly by fluoroscopy. If bronchospirometry is done concurrently, the examiner can satisfy himself that occlusion is total, for the oxygen uptake will then be completely abolished in the occluded lung He will also have an approximate measure of the proportion of the total blood flow that is diverted to the nonoccluded lung As a rule, we did not perform bronchospirometry coincident with the catheterization, since it greatly disturbs the basal conditions and complicates evaluation; however, we did perform it, in all cases, a few days before or after the other examinations, and the oxygen uptake then recorded was taken as a criterion of the degree of occlusion

The method generally involves no hazard aside from the conventional catheterization, nor does it cause the patient any distress The patients we studied were classified in two groups one in which the nonoccluded lung was judged to be quite free from pathologic changes, and one in which both lungs showed more or less advanced parenchymal lesions The two groups were similar with respect to the peripheral circulation Although in some cases up to 75 per cent of the total oxygen consumption as well as the pulmonary blood flow had been transferred to the non-occluded lung, neither the $O_2$ consumption nor the arterio-venous oxygen difference were altered Hence the cardiac output was maintained and the systemic arterial pressure remained quite unchanged This was true both at rest and under light exercise, and fully accorded with the results obtained in animal experiments (Lategola, *1956;* Frank et al, *1956*).

As regards the respiration, however, our results diverged from those reported in animal experiments In these latter, Bitter (*1956*) and Folkow & Pappenheimer (*1956*) showed that the total ventilation increased in proportion to the oxygen uptake which previously occurred in the occluded part of the lung, for this part naturally serves as an increased dead space In our tests, on the other hand, in which there was no local or general anesthesia, an increase of the total ventilation occurred only to a limited extent In cases where about 50 per cent of the oxygen uptake was occluded, so that the ventilation could be expected theoretically to rise by about 85 per cent, the observed rise in fact amounted to only 30 per cent This discrepancy may be attributable to the anesthesia and artificial respiration in the animal experiments, in which case it would point to an altered distribution of the respiratory volume, possibly due to increased bronchial muscle tonus in the occluded part of the lung

As regards the hemodynamics of the lesser circulation, the effect of unilateral pulmonary artery occlusion was all the more conspicuous, and differed in the two groups In both instances there was a significant rise in the pulmonary arterial pressure, and it was correlated to the oxygen uptake of the occluded lung In cases of virtually normal perfused lungs the rise was moderate, being of the order of 40 per cent on doubling of the blood flow.

In the group with parenchymal lesions, on the other hand, the rise was significantly greater, its order of magnitude was 70 per cent on similar doubling of the flow

In both groups the relationship was the same in examinations at rest and during exercise The results accordingly show a direct correlation between the

flow and the volume of the available vascular bed on the one hand, and the pulmonary arterial pressure on the other. Comparison of these investigations and those conducted by Lategola (*1956*) in dogs, in which he calculated the effective vascular area with a similar though more accurate method, shows very close agreement.

We have noted earlier that the ventilation-blood flow ratios in the lungs are often pathologically changed in pulmonary tuberculosis. The effect of these changes can be measured quantitatively with the method devised by Riley & Cournand (*1949*), based on high and low oxygen breathing for determination of the diffusion capacity. The venous admixture into the arterial blood that can be determined by this method is a criterion of the degree of ventilation-perfusion disturbances, and the venous admixture is known to be elevated in most cases of pulmonary tuberculosis. In our cases under study we have found values up to 30 per cent of the cardiac output. By combining this method with unilateral pulmonary artery occlusion it is possible, under certain conditions, to estimate the venous admixture in the occluded part of the lung. The method is appropriate in cases with extensive unilateral lesions, but in those with bilateral changes that respond with a high pressure to occlusion of one pulmonary artery the venous admixture often increases, probably reflecting a greater perfusion of poorly ventilated areas in that part of the lung. I will exemplify the method by outlining 2 cases that we studied both preoperatively and postoperatively (fig. 2).

The first of them concerned a 32 year old man who, in 1951, was found to have moderately extensive lesions of the left lung. The following year there was massive progression in the same lung. Not until 1954 would the patient agree to adequate treatment, and was then subjected to eight-rib thoracoplasty. The operation was followed by a complicating bronchial fistula, and a residual cavity was found. The preoperative examination had been carried out with respect to the possibilities of pneumonectomy.

Both at rest and during exercise the pulmonary arterial pressures were normal, but the arterial oxygen saturation was pathologically reduced. There was some elevation of the dead space ventilation. Of greater interest, however, was the low diffusion capacity (determined, unfortunately, only at rest) and the elevated venous admixture into the arterial blood.

On occlusion of the left pulmonary artery we found virtually no change in the pulmonary arterial pressures. The diffusion capacity was unchanged, but the venous admixture decreased markedly.

Follow-ups 12 months after the pneumonectomy showed, in principle, the same results as the preoperative examination with left pulmonary artery occlusion. The dead space ventilation, as was to be expected, had decreased. The diffusion and venous admixture were unchanged.

This case demonstrates both that the hemodynamics may remain practically normal in spite of widespread pulmonary lesions and that the disturbed ventilation-blood flow ratio in a so-called destroyed lung manifested as increased dead space ventilation and venous admixture into the arterial blood, can be quantitatively evaluated by pulmonary artery occlusion (fig. 3).

The second case relates to a 40 year old woman whose tuberculosis was ushered in with bilateral lesions as long ago as 1931. She had been treated with right and left ar-

to localize the tip exactly by fluoroscopy If bronchospirometry is done concurrently, the examiner can satisfy himself that occlusion is total, for the oxygen uptake will then be completely abolished in the occluded lung. He will also have *an approximate measure of the proportion of the total blood flow* that is diverted to the nonoccluded lung As a rule, we did not perform bronchospirometry coincident with the catheterization, since it greatly disturbs the basal conditions and complicates evaluation; however, we did perform it, in all cases, a few days before or after the other examinations, and the oxygen uptake then recorded was taken as a criterion of the degree of occlusion

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tificial pneumothorax, and in 1938 had been subjected to left thoracoplasty. Since 1954 there had been repeated relapses in the right lung.

The preoperative examination was designed to elucidate the possibility of resection of the right lung.

Examination at rest provided further confirmation of the disturbed ventilation-blood flow ratio that is often present in cases with extensive pulmonary lesions; but the pulmonary arterial pressure was normal. However, occlusion of the right pulmonary artery caused a substantial rise in pressure that was especially marked during light exercise, and at the same time the venous admixture rose. This had to be regarded as an increased perfusion of poorly ventilated areas and, together with the elevated pulmonary arterial pressure, indicated the patient's limited cardiopulmonary reserves.

Ten months after resection of the right upper and middle lobes, the patient once more underwent examination, which showed that she had tolerated the operation with a moderate further reduction of the cardiopulmonary function.

In this case the distribution of the pathophysiologic changes with respect to the two lungs was not determined. The investigation did show, however, the high degree to which the patient's cardiopulmonary reserves were being utilized even before the operation. Nonetheless, surgical treatment was feasible and showed good results, thanks to careful planning and limiting the resection as much as possible.

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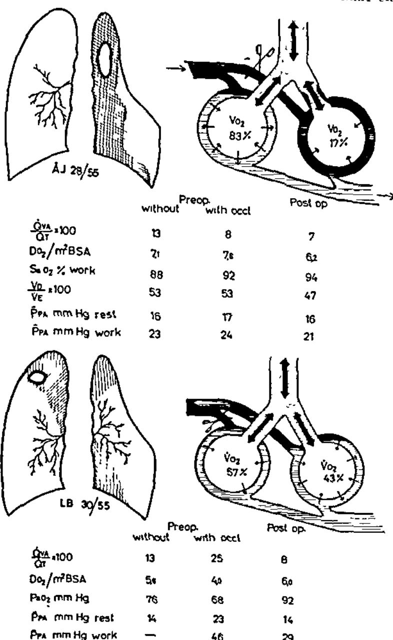
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| | Preop. without | Preop. with occl | Post op |
|---|---|---|---|
| $\frac{\dot{Q}VA}{QT} \times 100$ | 13 | 8 | 7 |
| $DO_2/m^2BSA$ | 7,1 | 7,8 | 6,2 |
| $SaO_2$ % work | 88 | 92 | 94 |
| $\frac{VD}{VE} \times 100$ | 53 | 53 | 47 |
| $\bar{P}_{PA}$ mm Hg rest | 16 | 17 | 16 |
| $\bar{P}_{PA}$ mm Hg work | 23 | 24 | 21 |

| | Preop. without | Preop. with occl | Post op. |
|---|---|---|---|
| $\frac{\dot{Q}VA}{QT} \times 100$ | 13 | 25 | 8 |
| $DO_2/m^2BSA$ | 5,6 | 4,0 | 6,0 |
| $PaO_2$ mm Hg | 76 | 68 | 92 |
| $\bar{P}_{PA}$ mm Hg rest | 14 | 23 | 14 |
| $\bar{P}_{PA}$ mm Hg work | — | 46 | 29 |

Fig 2.—(*top*) Physiologic measurements in a patient with unilateral lung disease

$\frac{QVA}{QT} \times 100 =$ Venous admixture as percentage of total blood flow

$Do_2/m^2BSA =$ Diffusion capacity for oxygen per square meter of body surface area

$Sa\ O_2\% =$ Arterial oxygen saturation

$\frac{VD}{VE} \times 100 =$ Dead space volume as a fraction of total volume of expired air

$\bar{P}_{PA} =$ Pulmonary arterial pressure

Fig 3.—(*bottom*) Physiologic measurements in a patient with bilateral tuberculosis

$PaO_2 =$ Arterial oxygen saturation (percent of normal)

Other abbreviations same as in figure 2.

# Effects of Lung Inflation on the Pulmonary Vascular Bed

*By* Richard L. Riley

In the following presentation I am acting as spokesman for Drs Solbert Permutt, John Howell and Donald Proctor. These men did the work and will present it before the American Physiological Society next month[1] I contributed concentrated thought and took part in some of the uproarious discussions

First I should like to present data on pulmonary vascular pressure and volume in relation to lung inflation, then show a model with which the experimental findings can be simulated, and finally draw inferences regarding the pressure surrounding the pulmonary vessels and airways

The first experiment which I shall describe started us on the track of one of the most intriguing physiological phenomena we have ever pursued The plan is shown in figure 1 The freshly excised left lower lobe of a dog's lung had the artery and vein cannulated and the blood in the system replaced by Dextran The vessels were then connected together by a T-tube and attached to a manometer The pressure in the vascular system at zero alveolar pressure was then adjusted, the level shown in the slide being 4 cm above the top of the lung Vascular volume was kept constant during lung inflation, by applying a known amount of positive or negative air pressure to the fluid in the vascular system Total vascular pressure during inflation therefore equaled the initial fluid level reading plus the amount added or taken away in the form of air pressure The bronchus was cannulated and, in the example shown, lung inflation was controlled by adjusting alveolar pressure The data which I shall first present were actually obtained with the lung placed in a tight box and inflated by negative pressure around it However, positive and negative pressure inflation are equivalent with respect to the amount of lung inflation brought about, and vascular pressure relationships are the same provided they are referred in both cases to the pressure surrounding the lung To avoid confusion, all studies will be presented in terms of positive pressure inflation

Figure 2 shows the changes in vascular pressure required to maintain constant vascular volume when alveolar pressure was changed Lung inflation is indicated by rising alveolar pressure The curve farthest to the left shows that, when the fluid level in the tube leading from the vascular system was 4 cm below the top of the lung at zero alveolar pressure, more and more suction had to be applied to the vascular system to maintain constant vascular volume as the lung was inflated This clearly suggests that the vascular system would have increased in volume had this tendency not been opposed by applying increasingly negative pressure The curve farthest to the right shows that

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when the pressure in the vascular system was 4.5 cm above the top of the lung at zero alveolar pressure, the vascular pressure had to be increased as the lung was inflated in order to maintain constant vascular volume. Vascular volume would have become smaller with inflation of the lung but for the increased vascular pressure. The central curve which runs close to the ordinate throughout the entire range shows that when the fluid in the vascular system was flush with the top of the lung at resting lung volume, there was little tendency for the volume of the vascular system to change during lung inflation. This experiment suggests that there is no simpler answer to the question, "Does the pulmonary vascular system get bigger or smaller with lung inflation?" The answer depends on the extent to which the vascular system is filled at the start of the experiment.

It occurred to us that these findings might be explained if the vascular system were made up of two compartments which responded differently to lung inflation. The following experiment suggested a way of testing this idea (fig. 3). When the excised dog's lung was perfused through the artery, fluid ran through freely when the lung was deflated but flow decreased progressively with inflation until a complete block was achieved. This pointed to the possibility that the alveolar capillaries were being squeezed shut by the alveolar pressure. If so, it might be possible to study the pressure-volume characteristics of the arteries and veins separately, using this tamponade technique to eliminate the capillaries from consideration. This proved to be the case, and with this technique it was shown that the volume of the arteries alone or of the veins alone increased with lung inflation. However, only the range of alveolar pressures above that required to produce tamponade could be studied. Eventually a blocking technique based on an entirely different principle was devised. It was found that kerosene could be introduced into the arteries or veins but would not pass through the capillaries even when a high pressure was applied. Using kerosene it was possible to determine the pressure-volume characteristics of the arteries and veins throughout the entire range of alveolar pressures. Studies with this technique are shown in the next slide.

Figure 4 shows the increase in the volume of the arteries and veins with lung inflation, at constant vascular pressure. Each isopleth represents a different level of vascular pressure, increasing from left to right. Note that the volume of the arteries and veins increased with lung inflation both at negative and at positive vascular pressures, in contrast to the behavior of the entire vascular bed as shown in the earlier slide. When vascular pressure was −16 cm. of water the arteries and veins were apparently sucked empty until the lung became moderately inflated. As vascular pressure increased, the absolute volume in the arteries and veins increased but the change due to lung inflation became less pronounced.

After the pressure-volume characteristics of the arteries and veins alone had been described, it became possible to estimate changes in capillary volume by taking the difference between the volume of the total vascular bed and that of the arteries and veins, at known values of vascular and alveolar pressure.

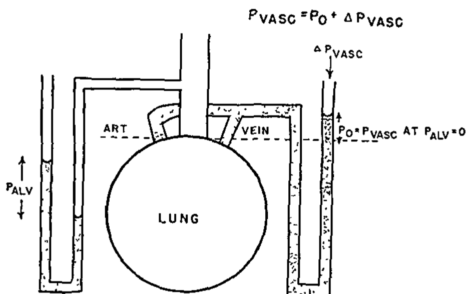



Fig 1—Schematic diagram of experimental technique

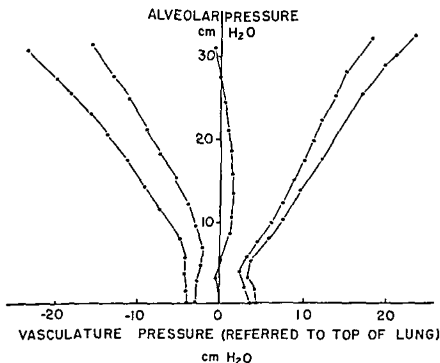



Fig 2—Vascular pressure required to maintain constant vascular volume plotted against alveolar pressure. Increasing alveolar pressure indicates increasing lung inflation

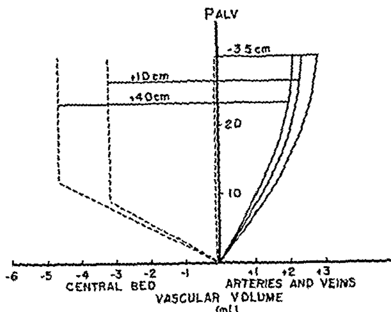



Fig 5.—Relationship between the volume of blood in the central bed and in the arteries and veins, and alveolar pressure

Figure 5 summarizes this information and contains the evidence which strengthened our belief that the pulmonary vascular system is divided into compartments which have opposite responses to lung inflation, causing the arteries and veins to increase in volume and the capillaries to decrease. The curves on the right differ from those of figure 4 in that the volumes in the arteries and veins have been added together and each curve starts from the zero point in order to show volume change rather than absolute volume. The curves on the left of the figure indicate that blood was displaced from the capillaries during lung inflation until alveolar pressure became high enough to empty the vessels. The amount displaced is believed to represent the volume contained in the capillary bed prior to inflation. Note that this volume was negligible at a vascular pressure of —3.5 cm. and increased markedly as pressure increased to +1 and then to +4 cm. Changes in the total volume of blood in the lung during inflation, although measured directly, are not shown in the slide. They can be calculated by taking the algebraic sum of the amount entering the arteries and veins and the amount leaving the capillary compartment. When vascular pressure was 3.5 cm. of water below the top of the lung, there was a net increase in blood volume with lung inflation, and when vascular pressure was 4 cm. above the top of the lung there was a net decrease. When vascular pressure was 1 cm. above the top of the lung the change in net volume was slight. These findings provide a satisfactory explanation for the original observations shown in figure 2.

Although in the performance of these experiments Drs. Howell, Permutt and Proctor experienced the pure and undiluted thrill of discovery, we must

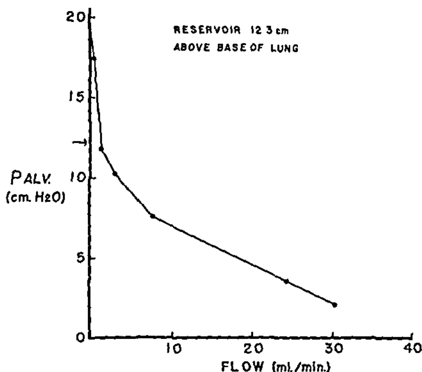



Fig. 3 —Relationship between pulmonary blood flow and alveolar pressure

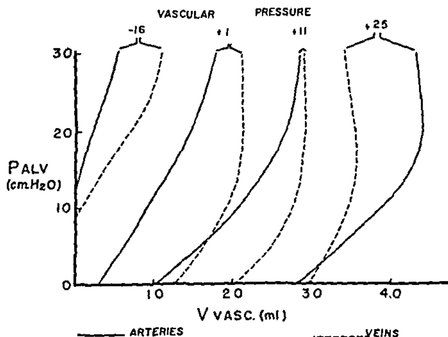



Fig. 4 —Relationship between the volume of blood in the arteries and veins, and alveolar pressure (lung inflation)

pass from a region of lower pressure to a region of higher pressure which contains the capillaries.

For simplicity we have used the term capillaries for the vessels contained in the region of higher pressure However, because the volume of these vessels is larger than that expected for capillaries alone, it seems likely that some of the small arteries and veins are also contained in the region which is compressed with lung inflation

Physiologists have been performing pressure-volume studies on the pulmonary vessels under conditions quite comparable to ours for almost 200 years, if one goes back to Haller's experiments in 1760[3] In spite of confusion on many points extending to the present, most people now agree that when the lungs are inflated with positive pressure, the vascular volume decreases and resistance to flow increases Findings to this effect by Quincke and Pfeiffer in 1871[4] were extended in beautiful experiments by Bowditch and Garland in 1879[5] They found that the changes were the same with either positive or negative pressure inflation provided the blood reservoir was inside the plethysmograph during negative pressure inflation These findings were repeated and confirmed in 1948 by Visscher[6] Remaining confusion seems to be related chiefly to the fact that when the blood reservoir is outside the plethysmograph during negative pressure inflation, there is a decrease in vascular resistance with lung inflation This finding is readily explained in the light of our studies The phenomenon of capillary narrowing with lung inflation was clearly described by Poiseuille in 1855[7] He studied the capillary bed histologically after injecting a congealing substance Priority in setting forth evidence for a two compartment system appears to go to Macklin, a mere 12 years ago in 1946[2]

No one to our knowledge has previously made the assertion, which we now make, that the arteries, veins and probably also the airways within the lung are surrounded by the equivalent of a pressure more negative than intrapleural pressure Our model shows that this can happen, and the experimental findings made the conclusion inescapable The capillaries, on the other hand, behave as if surrounded by a pressure closely approximating that in the alveoli We hope that these findings will not confuse the issue for the next 200 years

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concede that Macklin had described the major findings in 1946.[2] We find no previous record of anyone who studied the two parts of the pulmonary vascular system separately. Using a latex solution which would not enter the capillaries, Macklin studied the arteries and veins alone, much as we did using kerosene, and concluded: "that in inflation the volume of the arteries and veins of the mammalian lung is increased and in deflation it is decreased." Macklin also found that the capillaries, when filled with saline, could be collapsed by elevation of alveolar pressure.

We next set out to devise a model which would behave like the lung and, with luck, give us more insight into the mechanisms involved. Such a model is shown in figure 6. Dr. Leon Bernstein, who is now at the cardiopulmonary

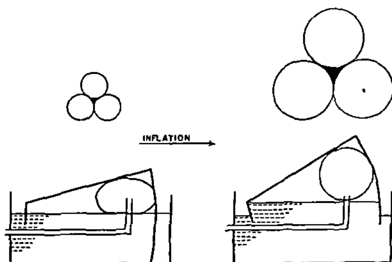



Fig. 6.—Schematic drawing of a model in which the changes in interstitial volume and pressure during inflation correspond qualitatively to the experimental findings in the lung.

laboratory at the Veterans Hospital in Baltimore, built us this Krogh spirometer out of transparent plastic. The spirometer contains a balloon which can be inflated and a small amount of trapped air. When inflated, the balloon pushes up on the inner wall of the spirometer, and the pressure of the trapped air outside the balloon becomes negative. This is because of the geometrical necessity for the space around the balloon to increase as the balloon enlarges. The aerial spheres appearing above the Krogh spirometer in the slide represent another attempt to demonstrate the same phenomenon. When the volume of the spheres increases, the space between them must also increase in volume. If the capillaries are considered to reside inside the balloon in the spirometer, they will be compressed as the lung is inflated, and if the arteries and veins are considered to be coursing through the space surrounding the balloon, they will be expanded as the lung is inflated. With this model it is possible to simulate all of the experimental findings. Somewhere within the substance of the lung are regions which act like the balloon in the model and other regions which act like the space outside the balloon. At some point the arteries and veins are believed to traverse a boundary corresponding to the balloon and to

because they are too small You are up against the interfacial tension between kerosene and water, and if the pressure is not great enough the kerosene will not go through It is like trying to push a bubble through a very tiny microinjection needle Therefore what the method is measuring, by the ingenious subtraction of Dr Riley, is *not* the volume of the *capillaries, but the volume of the bed which is in the vessels below a certain size*

It seems to me this leads one to conclude the opposite of what he does He concludes that, in a given case, the capillary volume decreases It seems to me that what the experiments prove is that the volume of vessels below a certain size gets less His results could indicate that the capillaries have become wider, so that the kerosene moved a little further into them Thus I think this most ingenious and most interesting work, on which I congratulate the authors, has to have a great deal of digesting before we agree that their interpretations are correct I would indeed congratulate the authors on a most stimulating paper

RILEY Dr Katz assures me this is an amazing amount of agreement to obtain from Dr Burton

We certainly did not mean to imply that one simulates in any exact way the actual breathing process when one has the reservoir either inside the plethysmograph or outside the plethysmograph because actually vascular pressure changes during the breathing cycle, but we have attempted to show the basic factors which determine the relationships We find simply that the pressure *inside* the alveolar capillaries is whatever the head of pressure is in the static condition, and that the pressure *outside* the alveolar capillaries appears to be simply alveolar pressure As you raise alveolar pressure in relation to the pressure inside the capillaries, adjusted in relation to any zero point you want to take, when the pressure on the outside gets higher than the pressure on the inside, the capillaries are squeezed shut and a complete block is achieved

Incidentally, we found we were then able to study the larger vessels without using kerosene at pressures above that required to achieve the complete block so that the studies using kerosene simply confirmed the studies using pressure block of the smaller vessels, and were not in any way conflicting They extended the range

I thoroughly agree that we do not have evidence as to exactly which smaller vessels are included in our central compartment I believe this compartment does contain more than just the capillaries because the volume which can be expressed during inflation is larger than one would expect to find in the capillaries alone

We are not trying to simulate true life with this model but to do just what Dr Burton loves to do—to simplify the problem so that we can look at it and see what the basic factors are and, particularly, in this instance, what the proper transmural pressure is

Obviously that is of the greatest importance and although this is a study on vessels, we have every reason to believe, from what we know of airway function, that the airways, like the arteries and the veins, are traveling through this space outside the balloons and are therefore subjected to a negative pressure which is more negative than intrapleural pressure

## Discussion

Chairman Werkö. I would like to ask Dr Burton if he has any comments.

Burton Of course, I have lots of comments, but I had better keep them for some other occasion

Dr Riley has tried to trap me. I have to admit the pressure in this spirometer does go negative He thinks that if I admit that, people will think I agree to all his conclusions On the contrary, though I feel that it is a very nice model, I am not surprised at, and the physicists would predict, what happens Yet I don't admit that this has anything to do with the lungs in the thoracic cage

I would begin to admit that it was related, if, when I took an inspiration, my lungs forced out my ribs, but I don't believe they do that So I really think that the model is very interesting and a nice thing to argue about, but it is not really related to respiration

I feel that for this work of Dr Riley, we ought to be grateful to him It is interesting and original, and will keep us busy for a long while arguing about it However, I want to raise one or two points I would be very foolish to stick my neck out right now, because obviously Dr Riley has spent much more time arguing and thinking about it than I have

There are two points that strike me at once First of all, the general results, without separating the capillaries from the rest of the vascular bed, it seems to me are in general agreement with the ideas I spoke about yesterday Dr Riley did mention the point which is often glossed over, that there is a tremendous difference, whether the perfusion pressure head is in the space subjected to negative inflation, or outside that space

Dr Visscher raised this point recently The point at issue really is which of these two conditions, the one where you put the pressure head outside the box, or where you put it inside, represents the respiration in the closed chest.

I myself am inclined to the idea that the normal respiration is much more like the case where there is a constant head of pressure, which does not share in the drop of intrathoracic pressure during inspiration It is somewhere in between this case and the other It seems to me the pulmonary artery is protected from the negative pressure to some extent, and the pressure does not fluctuate as much as the intrathoracic pressure, which it would if it were analogous to the perfusion bottle in the box

When we come to Dr Riley's ingenious experiment, in which he claims to separate volume of the capillaries from that of the arteries and veins, by the use of kerosene, I wonder whether there isn't perhaps a fundamental fallacy here. You see, he finds that the kerosene "will not go through the capillaries" Now, the word 'capillary' describes a geographical location from a morphological standpoint. We say these vessels are 'capillaries' but I think we have to ask ourselves why didn't the kerosene go through the 'capillaries'? It definitely was not because the capillaries possessed some distinctive chemical quality which repelled kerosene

The obvious answer is that kerosene will not go through the 'capillaries'

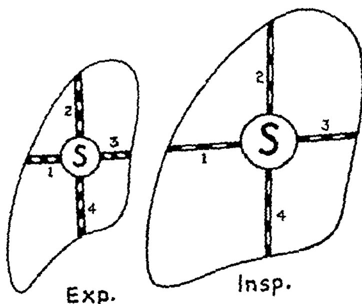



FIG 1—Effect of inspiration on an artery or vein, "S," and on the capillaries that lie within the elastic walls of alveoli (1-4)

both upon "S" and upon the pleura When the size of the lung is increased in inspiration, the elastic fibers are put on greater tension, whereupon the pull upon "S" becomes greater, tending to increase its size Arteries and veins therefore, tend to become larger in inspiration, provided that more blood is available to them

On the contrary, since the capillaries lie *within* the elastic fibers, they become elongated and flattened, as these fibers are subjected to the inspiratory stretch and consequent thinning This flattening may be sufficient to result in squeezing out of blood

FORSTER We have, of course, been interested in what happens to the capillary bed at different lung volumes and this was one of the measurements we made with the diffusing capacity for carbon monoxide We found there was very little change in $D_L$ over the normal range of variation in lung volume Now, one fly in the ointment is that Dr Gaensler's group in Boston have found a greater change, *i e*, a decrease at increased lung volumes

There are statements somewhere in the literature, that on lung inflation the capillaries as well as the veins would be distended by the supporting tissues pulling on them I believe this is unreasonable and I am therefore delighted to hear Dr Riley's ideas, although it will be several months before I can digest them I was very gratified to see Dr Liebow come out with his simplified diagram, which certainly presents my conception of the anatomical relationships of the capillaries and also predicts the changes in the pulmonary capillary bed with changes in alveolar volume which appear to me most reasonable

CHAIRMAN WERKO For a couple of years Dr Fishman has been playing

COURNAND · I wonder whether observations reported by Dr. François Franck in the *1880's* (1. François-Franck, Ch A, Nouvelles recherches sur l'action vaso-constrictive pulmonaire du grand sympathique Arch. Physiologie, 7 774-816, 1895.) may not fit in with the concept which you have just presented By stimulating the first thoracic ganglion, in order to identify its vaso-constrictive action on the pulmonary artery, the French physiologist observed a pressure rise in the pulmonary artery and a pressure drop in the left atrium This fitted with constriction of the vessels in some part of the pulmonary or capillary system However, simultaneous oncographic measurements of an exposed lobe, *demonstrated that its volume was increasing at the time of the* stimulation, whereas a reduction was expected to go along with arterial or capillary vaso-constriction. In order to explain this paradox, François-Franck suggested that the increase in the volume of the preparation was related to an increase in blood volume of the distensible large branches of the pulmonary artery which more than balanced the reduction in blood volume due to the constriction of the smaller vessels

RILEY · Yes, of course, it is true that you can explain any change in the total vascular bed, when you have one part of it getting bigger and the other part simultaneously getting smaller, but it appears, in our experience, to be what is actually happening In this situation the hydrostatic pressure in the capillaries is a very major factor because it is so much higher at the base of the lung than at the apex in the upright position Therefore, the capillary pressure at the apex may be less than the alveolar pressure and those capillaries may therefore be collapsed It takes more and more collapsing pressure to compress the capillaries as you approach the base of the lung because the pressure inside those capillaries is higher by the amount of hydrostatic pressure With lung inflation we do feel reasonably sure that there is a tendency for the capillaries to be more and more narrowed if vascular pressure is kept constant

SPAIN I realize it is presumptuous of me to get involved in a *biophysical* question but wouldn't the human situation be more closely approached if the outer compartment of your model was elastic and not rigid You are assuming that in humans there is a rigid compartment around the larger vessels—but this is most likely not so In a model with an outside elastic compartment the results would not be so neatly divided into two separate spaces Also it should be remembered that there is muscle in the larger vessels which is there for a purpose, probably to maintain the tone of the vessels and this would tend to counteract some of these other physical influences

LIEBOW The simple mind of the pathologist can find an explanation of some of Dr Riley's observations by reference to a model (fig 1)

The effect of increasing the size of the lung upon an artery or vein (indicated by "S") and upon capillaries (shown as minute circles within the walls *of the alveoli), is illustrated* The lung is shown in frontal section as if composed of only four alveoli, the elastic walls of which 1, 2, 3, and 4, insert upon the pleura and upon any structure such as "S" which they hold in suspension. This elastic tissue is always on a stretch There is a constant pull, therefore,

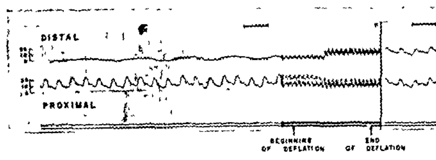



FIG 1 —The effect of acute occlusion of the right pulmonary artery on blood pressures distal and proximal to the occlusion

pressures presumably exist in the left atrium Despite these low pressures, the aspiration of 20 to 40 ml of blood across the pulmonary capillary bed is readily accomplished The ease of sampling suggests that there is no closure of some vascular segment beyond the balloon This type of observation has led us to believe that if a "critical closing pressure" for the lung vessels does exist, it is probably exceedingly low

CHAIRMAN WERKO Dr Fishman, in those cases you had a pressure of 5 mm Hg beyond the balloon?

FISHMAN Usually 5 to 7 mm

CHAIRMAN WERKO What was the pleural pressure?

FISHMAN We have nothing on the pleural pressure

CHAIRMAN WERKO It would appear that the pressure is higher than 5 mm Hg if the pleural pressure is below atmospheric

BURTON One point I would like to reiterate is that if we have vasomotor tone (about which we were talking yesterday) then I think the critical closing pressure is bound to rise considerably If this occurs, I am very puzzled about the problems in the lung of keeping all the vessels open, because of the very low pressures in the system

with the same balloon in unilateral lung disease as Dr. Riley and Dr. Söderholm, and I will ask him if he has some comments

FISHMAN: This paper of Dr Söderholm is an admirable example of the use of physiologic methods for the analysis of a complex clinical problem. Rather than attempt to make general comments about such a comprehensive review, I should like to concern myself with only one aspect of his study, i e. the physiological consequences of inflating a balloon so as to occlude one pulmonary artery

Our experience, gained in collaboration with Drs M Brandfonbrener, A Himmelstein and G M Turino, was gained during measurements of bronchial collateral blood flow in patients with unilateral lung disease.

Certain of our observations are in line with those of Drs Soderholm, Nordenstrom, Brofman, and others who have inflated a balloon in one pulmonary artery For example, as long as one lung is normal, occlusion of blood flow to the disease lung raises blood pressure in the main pulmonary artery *by only a few mm Hg Moreover, as illustrated in figure 1, distal to the balloon* the blood pressure falls to a level generally associated with left atrial pressures, and the record assumes a pulmonary "wedge" contour Finally, if blue dye or radio-opaque material is introduced distal to the balloon during complete occlusion, i e when the bronchospirometric record indicates cessation of oxygen uptake, the tracer substance remains in situ for a long while, only gradually leaking into the systemic circulation

However, I should like to stress other aspects of our study which are pertinent to two topics of today and yesterday bronchial collateral blood flow in bronchiectasis, and "critical closing pressure "

Dr Liebow has demonstrated large systemic-pulmonary artery communications in bronchiectatic lungs Consequently, we were rather disappointed that our own studies on patients with moderately severe bronchiectasis failed to show blood flows in excess of 600 ml per minute Moreover, blood samples *withdrawn from beyond the balloon were fully saturated with oxygen,* alkalotic, and low in $P_{CO_2}$ at a time when systemic arterial blood perfusing the collateral vessels was only 70 per cent saturated and normal in pH and $P_{CO_2}$ These values for blood gas composition, the absence of left ventricular hypertrophy, and the lack of a wide systemic arterial pulse pressure support the direct measurements by indicating that the collateral arteries are not pouring much blood into the diseased lung

These differences between the anatomic displays and the physiologic measurements are easily reconciled Dr Liebow is apparently demonstrating the collateral circulation in a lung which was virtually destroyed by chronic suppurative disease On the other hand, our values for collateral blood flow were obtained in patients with moderately severe bronchiectasis, who had been spared the complications of extensive destruction and fibrosis of the adjacent parenchyma, pulmonary distortion, pleural symphysis and mediastinal displacement

With respect to the "critical closing pressure," figure 1 illustrates that blood pressures beyond the balloon fell to a level of 5 to 7 mm Hg Similar

Except for vagal syncope in two patients who were standing waiting to begin exercise, there were no ill effects from this procedure

To indicate that pulmonary emphysema was present, it is desirable to note the abnormalities in the pulmonary function studies All patients were men between the ages of 40 and 60 years, with an average of 53 years For the sake of clarity and convenience we have rather arbitrarily arranged these 10 patients in the order of an increasing maximum breathing capacity with the lowest (13 per cent of predicted) being on the left, and the highest 55 per cent being on the right The solid bar represents the mean normal value, and the bracket sign, the range of normal In figure 1 the maximum mid-expiratory

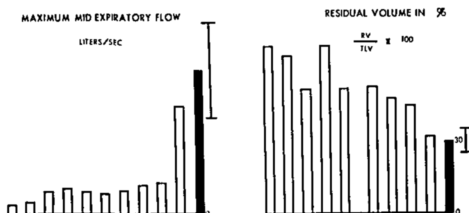



Fig 1 —Maximum and mid expiratory flow is shown on the left and residual volume as a percentage of the total lung volume is shown on the right

flow is shown on the left, and the residual volume as a per cent of the total lung volume is shown on the right It may be seen that one patient falls in the normal range in each of these studies The arterial oxygen saturation during exercise varied from 94 per cent down to 49 per cent and the carbon monoxide diffusion capacity in each instance was low This data has been presented to indicate that obstructive emphysema was present in these patients, and that the degree varied from mild to severe

Before discussing the results of the hemodynamic studies in these patients, it is well to review the range of cardiac outputs in normal subjects Figure 2 shows 92 studies on normal subjects as gathered from the published data of the authors shown and from unpublished data from our own laboratory All patients except those of Asmussen were studied by the Fick method during pulmonary artery catheterization The figures for blood flow and oxygen uptake are expressed per square meter of body surface area to provide a uniform basis for comparison The arterio-venous oxygen difference is related to the oxygen uptake and the cardiac index in accordance with the Fick principle, and lines of constant A-V difference (isopleths) having the values indicated along the top of the graph may be drawn through the origin As the severity

# Cardiac Output in Pulmonary Emphysema

*By* S. Gilbert Blount, Jr.

The cardiac output has been stated by some observers to be high in pulmonary emphysema particularly in those patients who have peripheral arterial oxygen unsaturation The right heart failure which may supervene has been reported to be a high output failure. The right ventricle then would be faced with the paradox of maintaining an elevated cardiac output in the face of an increasing pulmonary vascular resistance

The problem of the cardiac output in the patient with emphysema has been one of great interest to us since *1950*. In presenting these data before you today, I am acting as the spokesman for a group working in our laboratory on this problem Dr John Reeves has performed a very great portion of this work, Dr Robert Grover has also been an integral part of this team and last, but certainly not least, Dr Giles Filley Certainly, without the council and help of Dr Filley, much of this work would not have been possible

In *1951* we presented data here in Chicago before the Central Society for Clinical Research revealing that the mean resting cardiac index in 25 patients with pulmonary emphysema was 3 0 liters In reviewing the problem recently, it was noted that few exercise studies of emphysematous patients have been published Evaluation during exercise, however, would appear to be less affected by emotional factors, and to approximate more closely the demands placed upon the circulation by everyday life We therefore elected to study a group of patients with relatively pure emphysema, not complicated by heart failure, who represented a spectrum of the disease from mild to severe Ten men without detectable cardiac or pulmonary disease other than pulmonary emphysema were carefully selected for rest and exercise studies by cardiac catheterization techniques For exercise, walking on the treadmill was employed because it is a form of exertion familiar to the patient, and it is constant and predictable throughout the procedure

The study was initiated by passing a no 7 cardiac catheter in the routine fashion into the pulmonary artery of the unsedated patient Resting pressures and cardiac output were then obtained. The patient then walked to the adjacent treadmill, where exercise was almost immediately begun at a speed and grade previously determined. The arterial and venous intubation was performed in the same arm, and this arm was supported by a sterile arm rest during the walk. The electrocardiogram was monitored continuously Frequent pressure determinations and blood collections were obtained from the pulmonary and brachial arteries. Expired air was also collected at regular intervals The duration of walking varied between 6 to 10 minutes, and the Fick output measurements reported here were made during the fifth and sixth minutes

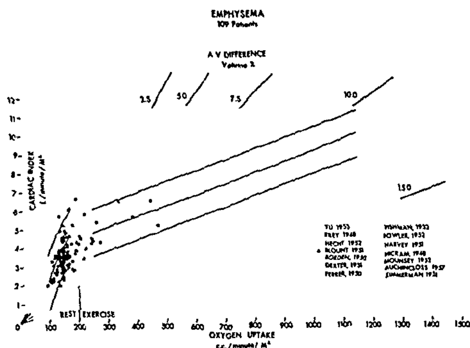



Fig 3 —Data showing cardiac output and oxygen uptake of 109 patients with emphysema

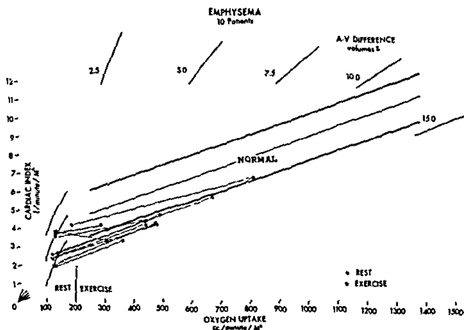



Fig 4 —Data similar to those of figure 3, obtained from 10 men with pulmonary emphysema

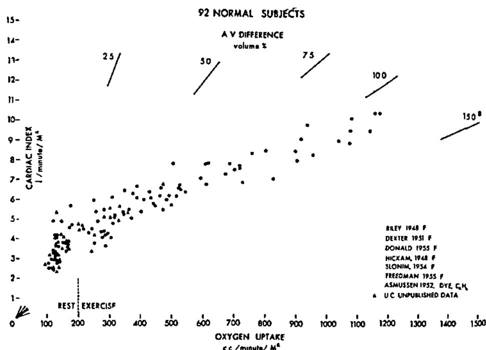



Fig 2 —The range of cardiac output in 92 normal subjects This material was gathered from published data of the authors shown

of the exertion increases, the oxygen uptake and the cardiac index increase in such a way that the exercise values fall along a relatively straight line A mean straight line drawn by the method of least squares through these exercise points, and lines representing two standard deviations above and below that mean are shown as a frame of reference on the two subsequent graphs For the resting values, a curved mean line was also drawn as well as two standard deviations above and below that mean A gap was purposely left between the rest and exercise means due to a lack of data in this area After plotting the data in this fashion, if for a given oxygen uptake, the patient has a high cardiac output, then the plotted value would lie above these normal values, and conversely, if the cardiac output were low, then the plotted value would *fall lower than these values Also it may be seen that if the cardiac output is* low, the arterio-venous oxygen difference is increased.

Figure 3 presents the data of 109 patients with emphysema, excluding those said to be in heart failure, as published by the authors who are listed in the lower right corner The lines indicating the mean normal and plus and minus two standard deviations are shown Here there appears to be a relatively wide scatter of resting values, with perhaps a greater concentration of points in the low normal range There are a few points above and a few below the normal range. Also the small number of patients who have been studied during exercise and the mildness of the exercise is shown

Figure 4 shows the data which we obtained from 10 men with pulmonary

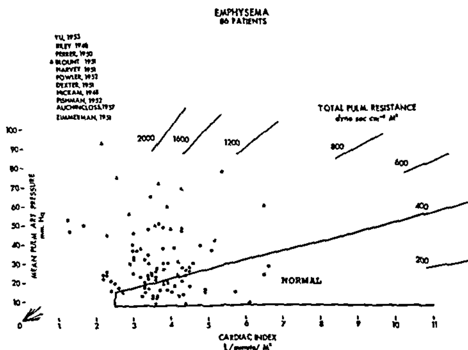



Fig 5.—The relationship between pulmonary artery pressure and cardiac index in 86 patients with emphysema from data published by the authors shown in the figure

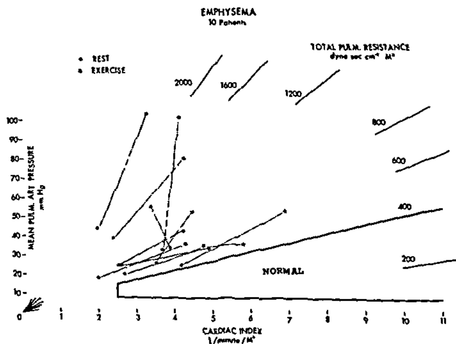



Fig 6.—Data similar to those shown in figure 5, obtained from 10 patients with emphysema.

emphysema recently studied in our laboratory The normal with two standard deviations is again shown. None of these 10 patients had a high cardiac index, and at rest most fall in the low normal range During exercise two lie in the low normal range, and the others are slightly more than two standard deviations below the mean The patient in the normal range whose exercise value lies farthest to the right was the one whose pulmonary function studies most nearly approximated normal It is of interest that the other patient in the low normal range during exercise had severe pulmonary emphysema, and his exercise point falls farthest to the left There is one patient whose cardiac index decreased with exercise. From these data it appears that the cardiac index tends to be low, particularly during exercise, and that the increased demand of the tissues for oxygen during exercise is partially supplied by increased oxygen extraction from the available blood

In figures 5 and 6 are shown the changes in the pulmonary artery pressure and resistance which occur in emphysema The pulmonary artery pressure is plotted against the cardiac index The total pulmonary resistance is mathematically related to the cardiac index and mean pulmonary artery pressure in such a way that isopleths of constant resistance having the values indicated may be drawn through the origin In normals the pulmonary resistance does not increase with exercise, but rather decreases in many subjects The perimeter of normal is outlined to serve as a basis of reference in the two graphs

In figure 5 are shown 86 patients with emphysema taken from the data published by the authors shown in the upper left corner No attempt has been made to indicate which are the resting and which the exercise points The scatter is great, but a large proportion of these values lie outside the normal range

Figure 6 shows the 10 patients we have recently studied indicating the manner in which the pulmonary artery pressure and resistance change with exercise in each case In all patients, the pulmonary pressure and resistance are elevated The changes during exercise in some patients tend to follow lines of constant resistance while some show even a slight decrease in resistance, and in this respect these patients approach normal behavior However, in 4 patients including the one with a falling output, a small change in cardiac output was accompanied by a large increase in pulmonary artery pressure and resistance This marked increase in resistance cannot be explained by increasing the flow in a rigid system It would appear then in some of these patients that there are mechanisms which act during exertion to further increase the pulmonary vascular resistance, which was already elevated at rest.

Because of the poor ventilation already shown in these patients and the relatively short period of exercise (6 to 10 minutes) which was tolerated, one wonders if a "steady-state" was reached and therefore if the use of the Fick principle was valid

Figure 7 presents the data from one of the more severely ill patients The top line indicates the mean pulmonary artery pressure and its response to exer-

## Discussion

FRITTS: Dr. Blount, you seem convinced that the elevation of the pulmonary arterial pressure could not be attributed to the effect of increased flow in a restricted vascular bed How can you be certain that this is true?

BLOUNT. Probably we shouldn't say we are certain of it, but if we assume this to be a rigid system with a fixed resistance, then although there might be a change of flow, or a change of pressure the resistance should not be altered

FRITTS: Since blood is not a homogeneous fluid, I doubt whether a vessel of fixed dimensions can be equated to a constant resistance to flow.

BLOUNT: We believe the increase in resistance in these patients to be due to other factors—the effect of hypoxia and the factor of the changing hematocrit in these patients must be considered The hematocrit rises with exercise, one patient comes to mind in whom the hematocrit rose from a resting value of 52 to 58 with exercise These and doubtless other factors have to be considered in the evaluation of the increasing resistance which occurs in these patients with exercise

DONALD· I would like to congratulate the author on his excellent presentation. I would also like to congratulate him on the excellence of his references

I would like to ask one question about the relationship between the resting cardiac output and the warmth of the hands. We have found that some patients with pulmonary emphysema have a slightly elevated cardiac output. On exercise we have found these people do not show the usual vasoconstriction in the periphery seen with emphysema I wonder if he has any observation about peripheral circulation in relation to the cardiac output.

BLOUNT· We have noted warm hands in an occasional patient and in one patient recently studied, despite the presence of warm hands and a striking capillary pulsation in the nail beds, the cardiac index was found to be about 2 liters This causes one to wonder about the status of the peripheral circulation to the extremities in some of these patients Most of these patients, however, did not have warm extremities

DONALD· In our experience hypercarbia has an important influence on the circulatory state of patients with emphysema Most of the patients with "high normal" cardiac outputs have some degree of carbon dioxide retention

Another interesting relationship is the frequency of polycythaemia in emphysematous patients with dilated and hypertrophied right ventricles These patients usually have gross distributional defects. Shortness of breath is not always a conspicuous feature in such cases.

DEXTER. I am very much interested in this paper of Dr. Blount's. There are one or two points I would like to raise for discussion

It seems to me that in any extensive pulmonary disease of this sort, one is confronted with two factors One is arterial oxygen saturation The other is increased pulmonary vascular resistance.

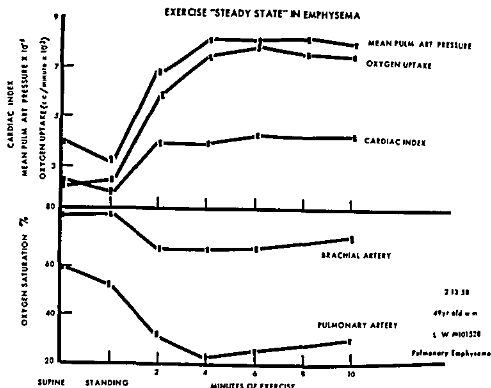



Fig 7 —Data indicating that a steady state was reached in this particular patient suffering from pulmonary emphysema

cise approaching and maintaining a steady level of 80 mm Hg at 4 minutes. In a like manner the oxygen uptake at rest, upon standing, and for each two minute collection period throughout the 10 minutes of exercise is shown It is noted to become fairly stable at about 700 cc. per minute after 4 minutes The cardiac index reveals a similar response at 4 liters per minute

The oxygen saturations in the brachial artery and the pulmonary artery are seen to drop promptly and then to rise slightly toward the end of the procedure. Although the data on all of the other patients are not so complete in each case, we believe that the cardiac index, oxygen uptake and pulmonary artery pressure are sufficiently stable after the fifth minute to make the Fick technique and calculations of pulmonary resistance reliable

Thus in conclusion these 10 patients with emphysema of varying severity revealed a normal resting cardiac output; in fact, most showed a low normal cardiac output.

The data here presented demonstrate a low and/or normal cardiac output in each patient during exercise In no instance was a high output found Also the cases studied indicate the presence of an increased vascular resistance, which during exercise, may in some cases increase, or decrease or remain unchanged.

## Discussion

FRITTS: Dr Blount, you seem convinced that the elevation of the pulmo arterial pressure could not be attributed to the effect of increased flow restricted vascular bed How can you be certain that this is true?

BLOUNT: Probably we shouldn't say we are certain of it, but if we ass this to be a rigid system with a fixed resistance, then although there migh a change of flow, or a change of pressure the resistance should not be alt

FRITTS: Since blood is not a homogeneous fluid, I doubt whether a vess fixed dimensions can be equated to a constant resistance to flow

BLOUNT We believe the increase in resistance in these patients to be d other factors—the effect of hypoxia and the factor of the changing hemat in these patients must be considered. The hematocrit rises with exercise, patient comes to mind in whom the hematocrit rose from a resting val 52 to 58 with exercise These and doubtless other factors have to be consid in the evaluation of the increasing resistance which occurs in these pat with exercise.

DONALD I would like to congratulate the author on his excellent pres tion I would also like to congratulate him on the excellence of his refere

I would like to ask one question about the relationship between the re cardiac output and the warmth of the hands We have found that some tients with pulmonary emphysema have a slightly elevated cardiac output exercise we have found these people do not show the usual vasoconstrictio the periphery seen with emphysema I wonder if he has any observation a peripheral circulation in relation to the cardiac output

BLOUNT We have noted warm hands in an occasional patient and in patient recently studied, despite the presence of warm hands and a stri capillary pulsation in the nail beds, the cardiac index was found to be a 2 liters This causes one to wonder about the status of the peripheral cir tion to the extremities in some of these patients Most of these patients, ever, did not have warm extremities

DONALD In our experience hypercarbia has an important influence or circulatory state of patients with emphysema Most of the patients with " normal" cardiac outputs have some degree of carbon dioxide retention

Another interesting relationship is the frequency of polycythaemia in physematous patients with dilated and hypertrophied right ventricles T patients usually have gross distributional defects Shortness of breath is always a conspicuous feature in such cases

DEXTER: I am very much interested in this paper of Dr. Blount's Ther one or two points I would like to raise for discussion

It seems to me that in any extensive pulmonary disease of this sort, o confronted with two factors One is arterial oxygen saturation The oth increased pulmonary vascular resistance

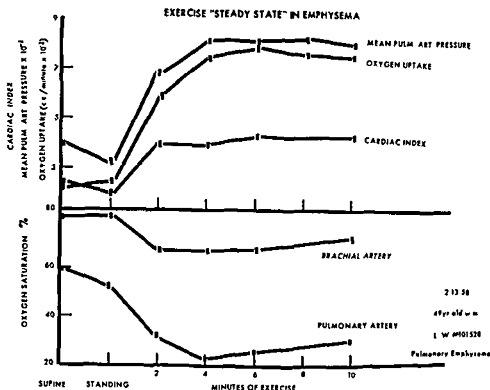



Fig 7 —Data indicating that a steady state was reached in this particular patient suffering from pulmonary emphysema.

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gists at this time whether they can give us any information as to what elastic stains do show in emphysema particularly in these very fine air ducts just before the alveoli.

SPAIN I know of no reported extensive and careful studies on the exact state of the elastic tissue in a large group of cases of emphysema, but I believe the alterations are variable and not consistent so that all sorts of arguments about pathogenesis have arisen

As yet the controversy is unresolved as to whether in some cases the process starts with, as you say, a loss of elastic tissue in the alveolar walls and that this is the cause of the difficulty or whether it actually starts in the bronchial tree with resistance to airflow as the prime mechanism

WOOD I think that the thesis of high cardiac outputs in cor pulmonale was put forward by McMichael, Sharpey-Schafer and Howarth in about *1915*, and that everyone has been resisting it ever since.

It seems to me that Dr Dexter said something which hasn't really been answered the lower the arterial saturation, the higher the pulmonary vascular resistance, so you won't find a high output in emphysema unless you happen to pick one with a low resistance That is what Dr Dexter said.

Now then, when the pulmonary vascular resistance is normal in cor pulmonale, and the arterial oxygen saturation low, is not the cardiac output high? This situation was found in about 10 per cent of my own series

Patients with diffuse carcinomatosis of the lung can have very high outputs with low resistances In these cases, however, there are often deposits in the liver, and the high output may be attributed to the hepatic state. I wonder if anyone has some information about the output when there are no deposits in the liver? I should add that any clinician should be able to distinguish between pulmonary hypertensive cor pulmonale with high resistance and hypoxic cor pulmonale with high output and relatively low resistance.

COURNAND May I first comment on the data, indicating a low cardiac output during exercise You will note that the rate of increase of cardiac output from rest to exercise in relation to work as measured by $O_2$ uptake, is about the same, as would be expected in normal subjects, with one exception, in which the validity of the measurement is questionable I wonder also in what age range were your subjects, since there is definite evidence that cardiac output in the basal state decreases with age.

Also I take great exception to the validity and meaning of the data concerning pulmonary vascular resistance obtained during exercise Anyone who is familiar with the pulmonary pressure pulse records, so markedly influenced by ventilation in these patients, should, I believe, accept such calculations with skepticism

Finally, with regard to the pulmonary pressure rise, in the range of exercise which you used, it is very small in normal subjects, although the cardiac output may be more than double its resting value

BLOUNT The ages of these patients varied between 40 and 60, with a mean of 53 years

I think there is *general agreement that an increased cardiac output does* not occur until the arterial oxygen saturation is below about 80 per cent, at which point cardiac output rises.

An increased pulmonary vascular resistance tends to decrease cardiac output. Thus, these two factors play against one another. In your patients, there was a variable degree of both arterial oxygen unsaturation and an increase of pulmonary vascular resistance.

It seemed to me that in one of your slides there were three patients whose arterial oxygen saturations were fairly low, the others being in the high 80's *or low 90 per cent ranges, where there should be no effect on the cardiac* output.

I have had a very limited experience in studying the response of such patients to exercise, but what little I have had, I have found very difficult to interpret because of the further fall of arterial oxygen saturation

Now when you say that the cardiac output in emphysema is not increased and is, indeed, somewhat low, it seems to me that this statement must be qualified by pointing out the relative effect of the two variables—arterial unsaturation producing an increased output and raised pulmonary vascular resistance *producing a reduced cardiac output The relative preponderance of one over* the other determines the given value

One other point is the effect of posture Most studies with exercise have been performed with the patient recumbent In your studies they were upright I remember an early report by Dr Riley et al (Am J Physiol, *152*:372, 1948) in which exercise in the upright position produced no increase of pulmonary arterial pressure, and yet in recumbency many have shown a very definite increase in pulmonary arterial pressure as a result of exercise to the same degree Thus, the effect of posture seems to have a very definite *effect on the response of pulmonary arterial pressure but not of cardiac* output for a given amount of oxygen consumption

I can't in a quick moment analyze what effect the upright position of your patients would have in comparison with the response of similar patients in recumbency reported in the literature, but I wonder if you could comment on this point

BLOUNT We can only speak relative to the particular patients whom we have studied Their emphysema was of varying severity as we have demonstrated One had a peripheral arterial saturation of 49 per cent. This patient *had a low resting* cardiac output and an inadequate response to exercise as did all of these patients

COMROE My question concerns the nature of airway obstruction in emphysema I think that the pulmonary physiologists have come to a concept of increased airway obstruction during expiration that is related to destruction of elastic tissue, not only in the alveolar walls, but also in *the fine air* ducts just before the alveoli We speak of this latter glibly and say that it results in a check valve mechanism but I for one don't really know what the pathological sections of this particular tissue show I would like to ask the patholo-

# Decompensated Pulmonary Heart Disease with a Note on the Effect of Digitalis

*By* M. Irené Ferrer and Réjane M. Harvey

At the present time, there is no universally accepted definition of chronic cor pulmonale or pulmonary heart disease Our group at Bellevue Hospital however is of the opinion that cor pulmonale should be taken to mean heart disease secondary to diseases of the lung. The crux of this definition lies in the demonstration of cardiac enlargement, either dilatation and/or hypertrophy, in association with a pulmonary disease known to be capable of compromising right ventricular function

Several further points require emphasis at this stage of our knowledge of cor pulmonale Perhaps in years to come these concepts will require re-evaluation or modification but at present, in order to stimulate clarity concerning present data or the acquisition of future data, they must be formulated From the definition just stated it is clear that the mere presence of *any* form of chronic lung disease and right heart failure is insufficient evidence for a diagnosis of cor pulmonale. It is becoming abundantly evident that the great majority of patients with cor pulmonale suffer from anoxia or anatomic compromise of the vasculature and that the suspected culprit, the lung disease, should therefore be one known to induce one or both of these causes of pulmonary hypertension Secondly, it is clear from such a definition of pulmonary heart disease that the presence of pulmonary artery hypertension per se does not constitute evidence of cor pulmonale Furthermore, it is now certain that all pulmonary disorders which induce mild or even moderate pulmonary hypertension do not necessarily go on to the complication of right heart involvement The right ventricle has great adaptability and pulmonary artery pressure elevation alone may not, ipso facto, precipitate a disturbance in its function An analogous situation obtains in the relationship of systemic hypertension to changes in the left ventricle Finally, this definition of cor pulmonale does not include patients with mitral stenosis or congenital heart disease even though it is known that lesions in the lungs exist in these cases, since their lung lesions are secondary to the basic cardiac disorders

In order to detail the features held to be characteristic of cor pulmonale, one must go back to the primary lung disorder to find the beginning of the natural history of the cardiac complication Thus a physiologic chart must eventually be constructed for each form of lung disease known to produce cor pulmonale, with indications as to the onset of circulatory disturbances Regrettably, data are woefully scant in all such diseases save emphy-

*The work described in this paper was supported by a research grant (H 2001 [C]) from the National Heart Institute of the National Institutes of Health, United States Public Health Service*

As regards the increase in pulmonary artery pressure, this was noted in each patient and one case showed a rise from a mean of 44 to 105 mm.Hg

Regarding the blood volume, the plasma volume in these patients was within normal limits as you have noted but the total blood volume was elevated in relationship to the increase in the red blood cell mass.

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of course the anoxia in this stage of recovery was still severe (a saturation of 83 per cent). The hematocrit on the second study was 54 per cent, an evidence that bone marrow had been continuously solicited by severe, although perhaps varying levels of anoxia. Thus from these data it seems justified to say that hypervolemia and elevated cardiac output as well as pulmonary hypertension may precede ventricular failure in this form of cor pulmonale

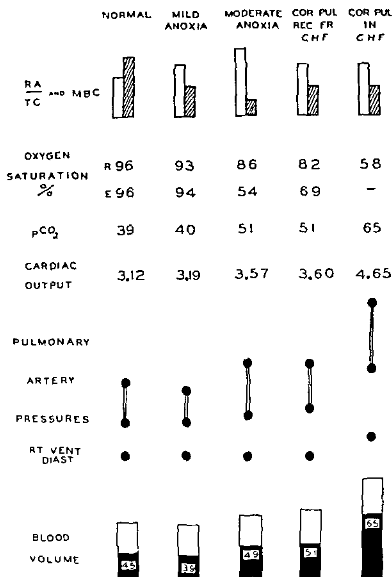



FIG 1 —Cardio pulmonary function in 21 patients with emphysema Circulatory alterations appear with the onset of moderate anoxia RA = residual air, T C = total lung capacity, M B C = maximum breathing capacity Cardiac output is here expressed in liters per minute per square meter B S A The numeral enclosed in the dark half of the blood volume here indicates the hematocrit For discussion see text

sema, the commonest cause of this disorder, and even here, there are still many gaps in our knowledge.

### Development of Cor Pulmonale Due to Emphysema

It has been our experience that in only two of the three forms of emphysema does circulatory dysfunction appear: in generalized "obstructive" emphysema with severe bronchitis, obstruction and anoxia, and in patients with minimum anatomic or physiologic evidence of emphysema but with severe bronchitis, bronchospasm and alveolar hypoventilation. In both these forms the element of bronchiolar obstruction with alveolar hypoventilation and consequent anoxia is paramount. In the third form, generalized "atrophic" emphysema characterized by fragmentation of elastic fibers and collapse of bronchioles but without bronchitis, significant anoxia (saturation below 90 per cent) is rare and cor pulmonale does not occur unless a complication in some of these subjects, air cysts become infected. In this state the bronchiolar tree is inundated with secretions, severe anoxia then occurs and cor pulmonale may follow.

Since the characteristic features of cor pulmonale secondary to obstructive emphysema include changes in arterial blood gases, cardiac output, lesser circulation pressures, and circulating blood volume, these were measured in a group of emphysematous subjects and are depicted in figure 1. These data, obtained at rest, suggest a certain sequence of events. When arterial oxygen saturation *at rest* falls below 80 to 85 per cent and carbon dioxide tension rises, one finds disturbances at the circulatory level. This can be seen on the chart where the cardiac output, pulmonary pressures and hematocrit all show increases with moderate anoxia as compared to the emphysematous group with mild anoxia. Other investigators have confirmed these findings[1] and emphasized especially the relationship between the degree of anoxia and the pulmonary artery pressures[2,3,4]. We have been fortunate, in our evaluation of the developmental alterations in the circulation, in being able to study some patients at two different stages of their disease, as have others[1,3,5,8]. Some recently acquired data of this kind are pertinent here.

In figure 2 (J.McC.) data of a 72 year old emphysematous subject are outlined. The first study was made before any heart failure had occurred. The absence of this complication is attested to by the fact that digoxin caused no change in the circulation (we have found that the output rises if failure is present). At first blush, one could say that although cardiac output and pulmonary pressures were elevated above normal, no other indications existed to suggest that right heart failure soon would follow. However, there is need for a second look at the data. On his routine pulmonary function studies, his arterial saturation during the 30 step (acute) exercise test fell from 91 to 67 per cent and his hematocrit, previously 47 per cent at the time of cathe-

measures directed at the pulmonary insufficiency but was not phlebotomized. He was restudied soon after recovery from failure. Comparison between evaluations shows that when he was on the way into failure the cardiac output was higher than when he had recovered from failure. The pulmonary pressures are the same as on the first study and

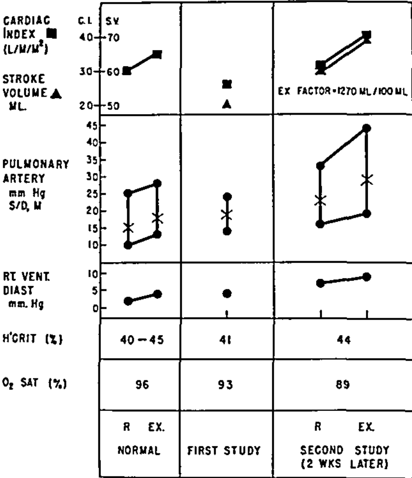



FIG. 3 —Hemodynamic data in a woman (A C ) with chronic cor pulmonale For discussion see text

deed precede clinical right heart failure in this woman as shortly thereafter she developed edema and hepatomegaly

Another series of observations (*B B.*, fig 4) starts with measurements in frank clinical right heart failure and cor pulmonale and includes two studies during the recovery phase. The cardiac output, already high, rises further with digitalization as the right heart filling pressure drops to normal Two weeks later, after great readjustments in the circulation have occurred following extensive therapy, blood flow is normal and remains so 4½ weeks later Some pulmonary hypertension remained on the second study however and the patient was still hypervolemic (hematocrit 69 per cent). Phlebotomies were then done between the second and third studies and with a fall in hematocrit to 47 per cent pulmonary pressures joined in the other normal circulatory functions.

From studies such as these made on patients with emphysema before right

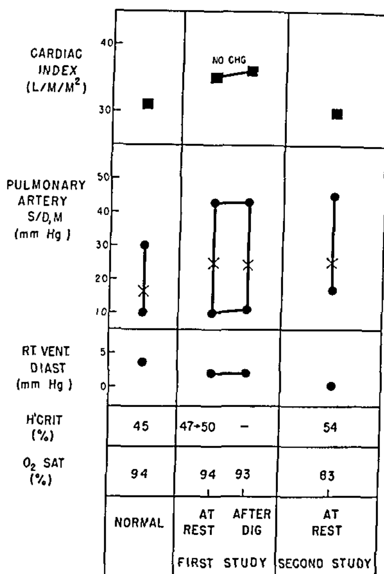



FIG. 2 —Hemodynamic data in a 72 year old male (J.McC) The first study was carried out before heart failure occurred, the second after recovery from failure.

Figure 3 (A C) offers similar evidence that blood flow, pulmonary artery and even right ventricular diastolic pressures may increase prior to clinical evidences of failure On her first study, although she had mild anoxia and hypercapnea, this woman's dynamics at rest were normal She was then allowed full ward activity and before discharge was again evaluated Her circulatory status had shifted into the next stage, namely output and pulmonary pressures had risen at rest, hematocrit was higher and arterial oxygen saturation lower. Most revealing was an elevated resting right ventricular diastolic pressure. On exercise all pressures rose further as blood flow increased in a normal fashion *This physiologic state of right ventricular strain did in-*

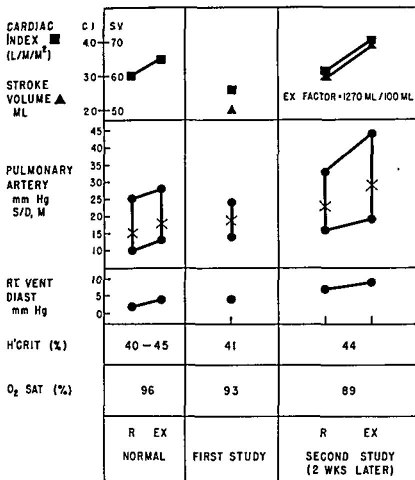



FIG 3—Hemodynamic data in a woman (A C) with chronic cor pulmonale. For discussion see text

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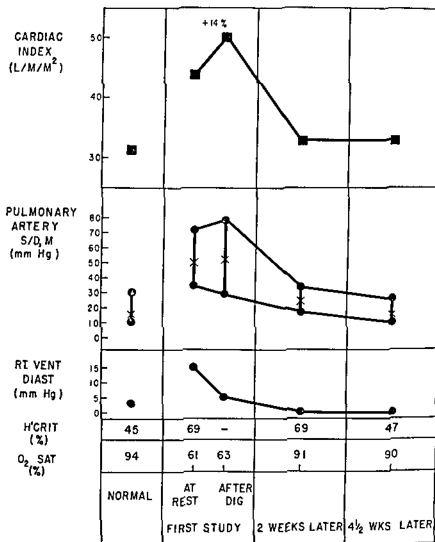



FIG 4 —Hemodynamic data in a patient (B B ) with chronic cor pulmonale For discussion see text

heart failure develops, during heart failure and after recovery from heart failure we can sketch the curve of blood flow and filling pressure in cor pumonale (fig 5) As the circulation changes prior to ventricular failure, output and ventricular diastolic pressure both rise (position 3 to 2) With the onset of failure, further increase in filling pressure occurs but with a reduction in flow (position 2 to 1) Digitalization can correct this, permitting a shift back from 1 to 2 as flow increases and filling pressure decreases On complete recovery from the state of cardiopulmonary insufficiency, the shift from position 2 to 3 occurs

This curve is placed in a range of normal blood flow throughout, except along the dotted line where flow is diminished This low level of blood flow (which we have seen develop in some patients) may represent a late phase of

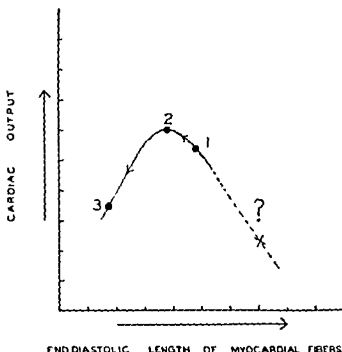



FIG 5.—A schematic curve relating changes in cardiac output and in myocardial fiber length at the end of diastole in cor pulmonale due to emphysema.

chronic or recurring right heart failure, while the higher levels of output in failure may indicate single acute episodes with little residual myocardial damage

### Level of Cardiac Output in Cor Pulmonale Due to Emphysema

The level of blood flow found in patients with cor pulmonale due to emphysema has been a subject of much discussion in recent years.[7 9 10] It is generally agreed that in most instances the level of blood flow in failure is higher than in patients with rheumatic or degenerative forms of heart disease and hence may be normal or even higher than normal. However, three studies[8 9 11] have revealed occasional patients with cardiac outputs in a low or even very low range at rest A recent study of 16 emphysematous subjects by Doctors Fritts and Chidsey in our laboratory has revealed the interesting point that in 4 the cardiac index lay between 2.2 and 2 3 liters However, 3 of the 4 subjects had never had evidence of cor pulmonale and are considered to have emphysema without cardiac involvement The anoxia was mild (the lowest saturation was 85 per cent) as was the pulmonary hypertension This study indicates that a low output may occur in emphysema without cor pulmonale Prior to the acquisition of this information a number of explanations were offered for the existence of a hypokinetic or low output state in pulmonary heart disease including absence of anoxia, high "pulmonary vascular resistance" or terminal condition of the patient.[8] The low cardiac output in the latter has certainly been seen Since a hypokinetic state may precede

cardiac involvement in emphysema, *factors other than those mentioned* may be involved

The only further point we would like to make concerning the level of cardiac output in right heart failure due to cor pulmonale is the directional change it takes when the patient moves from the state of congestive failure into recovery This information was gleaned from those reports in the literature [1,3 5,6,8] in which two such studies are given and in which the oxygen uptake in the two studies are comparable They were compared with a few cases of arteriosclerotic and hypertensive heart disease [12] With cor pulmonale *the output* usually *falls* with recovery from failure, as suggested in the Starling curve previously shown (fig. 5) In contrast the degenerative forms of heart disease usually show a rise or no change of output in recovery

## Level of Right Heart Pressures in Decompensated Cor Pulmonale

The concept that pulmonary hypertension is a major feature of decompensated pulmonary heart disease has been amply confirmed by many investigators In emphysema this pulmonary hypertension is a reversible one, springing, along with other circulatory disturbances, from anoxia and subsiding, even disappearing at rest, when the latter is corrected or mild A review of seven well documented papers reporting on cor pulmonale in emphysema [1,3 5 9] has yielded some very interesting data regarding the actual level of pressures found in patients in right ventricular failure due to this form of heart disease

TABLE I —*Range of Cardiac Output, Lesser Circuit Pressures and Arterial $O_2$ Saturation in Patients in Right Ventricular Failure with Cor Pulmonale Due to Emphysema (Data on 41 Cases Selected from Various Authors )*

| Authors | H' rit (%) | C O | C I | Pressures (mm Hg) Pulmonary artery Sys | Diast | Mean | Rt Vent diast | $O_2$ Sat % |
|---|---|---|---|---|---|---|---|---|
| Ferrer, Harvey, et al [1 5] (7 cases) | 42 70 | 4 2 10 0 | 2 69 6 06 | 49 90 | 23 38 | 35-57 | 9 17 | 55 86 |
| Mounsey et al [3] (13 cases) | — | — | 3 7 4 6 | 36 89 | — | | 6 20 | 25 87 |
| Ozcan, Hermanci, et al [6] (7 cases) | 55 62 | 6 0 9 2 | 3 8 5 1 | 49 86 | 25 46 | 38 63 | 7-18 | 50 78 |
| Denolin and Lequime [7] (4 cases) | — | 5 0 6 8 | — | 50 85 | | | 5 20 | 67 83 |
| Whitaker [8] (9 cases) | 44-58 | 1 9 8 1 | 1 1 4 3 | | | 37 59 | 5 16 | 56 72 |
| Fowler, et al [9] (1 case) | | | 2 1 | 92 | 50 | 59 | 17 | 51 |

As can be seen in table I the systolic pulmonary arterial and right ventricular pressures in failure may vary over a considerable range, 36 to 92 mm Hg, while the right ventricular diastolic pressure is elevated in a range of 6 to 20 mm Hg From these data it would seem difficult to relate the ventricular functional breakdown and failure solely to the level of pulmonary hypertension at rest, as it is not always severe A consideration of the behavior of the lesser circulation during exercise may clarify the role of pulmonary hypertension in the production of right heart failure, as one can then examine changes in both blood flow and pressure

## Response to Exercise in Cor Pulmonale Due to Emphysema

Regrettably there are very little data available on the response to exercise in emphysema and cor pulmonale We will present our own recently acquired information, although it is meagre.[12] It must be emphasized here that a steady state of exercise must be reached before a cardiac output by the Fick method can be validly measured, especially in the presence of the anoxic state

Several investigators have shown that pulmonary artery pressures rise on exercise in the emphysematous subject without cor pulmonale [13, 14] Insufficient data is available to state if all such patients also increase their cardiac output in a normal fashion One would assume that this is so, since the patient with emphysema who has recovered from right heart failure can do this

Once cardiac failure is present what response is found? Two different patterns have been observed to date The first of these is illustrated by a man in his first bout of frank right heart failure He showed (fig 6) elevation of his cardiac output and all lesser circulation pressures at rest but was able to increase blood flow in a normal fashion, while right heart pressures rose rather strikingly This is a state more properly called strain than actual failure in our view The second subject (fig 7) in his fourth bout of failure had a low cardiac output at rest and it was fixed on exercise, i e there was no increase at all The already elevated right ventricular diastolic pressure rose further. Since no more blood was passing through the lungs during exercise than at rest, the level of pulmonary hypertension did not change This performance suggests that a more advanced phase of cardiac insufficiency exists in this second case

Figure 8 depicts schematically what probably occurs in emphysematous subjects on exercise If failure is absent (column 2) the cardiac output can increase normally in the emphysematous subject regardless of whether or not there is any pulmonary hypertension at rest The increase in blood flow will raise pulmonary artery pressures, occasionally quite strikingly But if the right ventricle can tolerate this response its filling pressure does not exceed the normal during exercise

If the right ventricular filling pressure does rise during exercise (a in column 3, fig 8) even though blood flow increases normally or is eukinetic, an abnormal phase is present and physiologically this is probably where cor pulmonale begins

When the ventricular diastolic pressure is elevated at rest (column 4), clinically and hemodynamically it is obvious that a more advanced phase of cardiac dysfunction is present. Early in this phase the cardiac output may

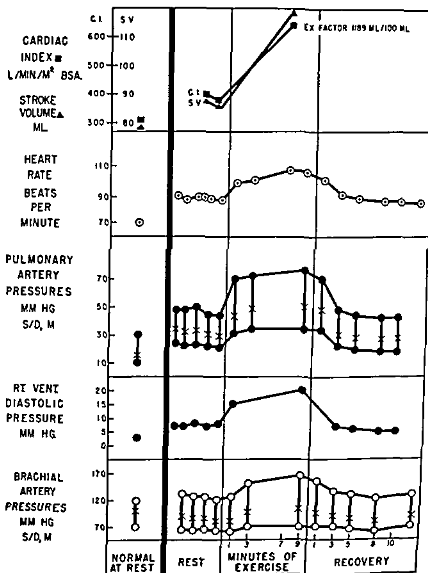



FIG 6—The response to exercise of a man (W W) in clinical right heart failure due to chronic cor pulmonale and emphysema For discussion see text

still increase normally on exercise. When the right ventricle can no longer increase its output normally on exertion (column 5) (and therefore is hypokinetic), or does not increase it at all above the resting level (column 6) (akinetic), the most abnormal phase of all has been reached

## General Concepts of Cor Pulmonale in Emphysema

Our concepts of the development of cor pulmonale and right heart failure in emphysema can now be summarized As a consequence of the underlying pulmonary disease, respiratory function may be so altered as to result in

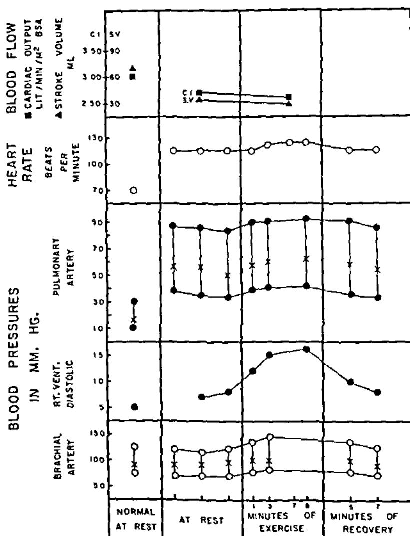



Fig 7—The response to exercise of a man (A P) in clinical right heart failure due to chronic cor pulmonale and emphysema. For discussion see text.

anoxia The latter condition of itself may effect an increase in cardiac output Anoxia may also be the initiating factor in the production of polycythemia and hypervolemia However, it is well known that many patients with chronic pulmonary disease and anoxia do not have polycythemia. Long term studies

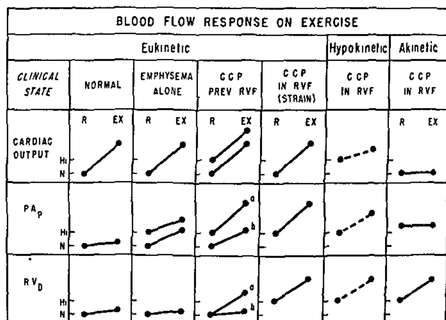



FIG 8 —Schema of the response to exercise of patients with emphysema with and without cor pulmonale For discussion see text

of these patients suggest that the duration and degree of anoxia are important in the production of this secondary polycythemia [12] Regardless of the exact mechanism involved in the production of polycythemia and hypervolemia, the latter may effect an increased diastolic right ventricular volume and thereby produce an increased stroke volume and cardiac output The ventricular muscle can maintain this increased output provided that the optimum value for the end diastolic stretch is not exceeded Obviously with the rising output of the right ventricle, there is an increasing venous return to the left ventricle and, in turn, its stroke volume also increases Possibly other factors, as yet unknown, may act to increase the cardiac output Another consequence of the chronic pulmonary disease is alteration of the pulmonary vascular bed which may be upon an anatomic or physiologic basis, or both The exact changes are not as yet clearly defined but may include a reduction in the area of the bed and reduction in the calibre of the vessels themselves or a decrease in the distensibility of the vessels The resultant restriction of the pulmonary vascular bed may be extensive enough to produce hypertension at rest because of the distortion of the normal pulmonary flow-capacity ratio However, it is apparent that the anatomic lesions, which are presumably not reversible, cannot be the sole factor in the production of pulmonary hypertension since the latter is reversible It would appear that in some cases at least, physiologic alterations must be superimposed upon the anatomic lesions before hypertension is produced Anoxia, by effecting vasomotor tone of the lung vessels and thereby further reducing the capacity of the pulmonary bed, polycythemia by increasing blood viscosity and hence increasing resistance to flow, may precipitate

or aggravate pulmonary hypertension even in the presence of a normal blood flow Any increase in the pulmonary blood flow in the presence of a restricted vascular bed would of itself produce pulmonary hypertension Many of the patients with chronic cor pulmonale have increased blood flow even at rest which, in addition to all of the other factors previously mentioned, would aggravate pulmonary hypertension The presence of anastomoses between bronchiolar and pulmonary arterioles must also be considered as a possible factor in the production of pulmonary artery hypertension.

Hypertrophy of the right ventricle may ultimately result from pulmonary hypertension When this chamber can no longer cope with the increased amount of work required of it, dilatation and eventual failure of this chamber result It is an essential part of this concept that dynamically the left ventricle remains normal and therefore is still able to empty itself efficiently in the presence of an increased venous return In some cases a sudden and marked increase in anoxia, presumably by a direct effect on the strained right ventricular myocardium, may precipitate cardiac dilatation and failure. The element of hypervolemia may also play a role in the production of failure by increasing the diastolic volume of the right ventricle to the point where the optimum diastolic stretch of the muscle fibers has been exceeded

It has been shown that the failing heart in cor pulmonale increases its output and lowers its filling pressure in response to digoxin (position 1 to 2, in fig 5), and that when the heart goes into failure the cardiac output is lowered from a previously higher level (position 2 to 1 or 1 to X, fig 5) The paradox of a normal or high cardiac output in the presence of failure can be explained by the fact that in chronic cor pulmonale the ventricular fibers are relatively intact as compared to those in patients with intrinsic myocardial damage such as is found in coronary artery disease, rheumatic myocarditis, etc The ventricles are therefore able to sustain a high cardiac output not only before failure ensues but even in its presence However patients with cor pulmonale in failure at the end stage of their disease, when the myocardium may be impaired, may have cardiac outputs even lower than normal (point X, fig 5)

In the analysis of the various factors operating in the production of chronic cor pulmonale, no attempt has been made to define the relative importance of any one mechanism It is obvious that these mechanisms are all interrelated and the importance of each may vary from patient to patient In the matter, for example, of the production of cardiac failure, the evolution may be gradual and progressive as a result of prolonged and sustained pulmonary hypertension or may be acute as a result of a sudden increase in anoxia secondary to bronchiolar obstruction associated with respiratory infections It has been frequently noted that patients with cor pulmonale will go rapidly into cardiac failure with infections which do not involve the respiratory tract. It may well be that the increased cardiac output generally associated with fever is sufficient to increase pulmonary hypertension acutely to such a degree that the right ventricle fails

The need to invoke a separate myocardial factor such as cryptic arteriosclerotic heart disease as suggested by Hecht [15] is not necessary to explain the

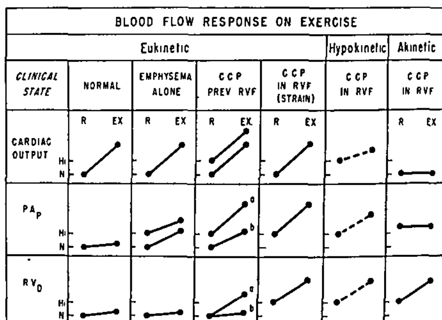



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membrane. Among these are berylliosis, Boeck's sarcoid, scleroderma, and certain granulomatous lesions and reticular fibroses of undetermined etiology. In these individuals pulmonary hypertension and right heart enlargement may be present before even moderate anoxia appears at rest; therefore, it seems likely that anatomic lesions are primarily responsible for this type of cor pulmonale. Undoubtedly, as the disease progresses and severe anoxia appears, its effects are superimposed. If anoxia becomes severe these subjects will even develop polycythemia.

## A Note on Digitalis in Cor Pulmonale

Following our report in *1950* [1] that digitalization was capable of increasing cardiac output in cor pulmonale, as well as affecting a fall in right ventricular filling pressure and a slight rise in the systolic pressure of this ventricle and the pulmonary artery, a number of investigators have repeated and confirmed our studies [3 6 19 20] No such effects, indeed no changes at all if one excludes the systemic artery, are noted if the right ventricle is not failing. This last statement includes the patient with cor pulmonale recovered from failure or the patient with only pulmonary hypertension who has not been in failure

It is of course apparent by now that digitalis alone cannot relieve the patient of his circulatory disturbances and hence it is only one of many therapies [21] we exhibit to subjects with decompensated pulmonary heart disease

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known facts. Indeed all of our cases who have come to autopsy have been free of any such evidence

## The Development of Cor Pulmonale in Other Forms of Chronic Lung Disease

Not every form of chronic lung disease produces cor pulmonale and indeed aside *from emphysema in one of its forms, very few do The circulatory* complications associated with kyphoscoliosis [16] are related either to an accompanying emphysema or to the hypoventilation syndrome initiated by faulty chest mechanics. Alveolar hypoventilation is at the core of the disturbances which lead to cor pulmonale in emphysema. There are other diseases in which this alveolar hypoventilation occurs, as for example in patients with poliomyelitis and those with extreme exogenous obesity (Pickwickian syndrome). At all events anoxia is again the offender common to all these conditions

Cor pulmonale, i e right heart involvement, is not seen as a result of uncomplicated bronchiectasis, lung abscess or pneumonia. If any of these diseases result in an accompanying form of emphysema with anoxia, or if anoxia occurs with a massively involved lung in pneumonia, right heart failure may follow. Similarly, uncomplicated pulmonary tuberculosis does not produce cor pulmonale even with extensive destruction of the parenchyma, although in some few cases [17,18] mild pulmonary hypertension at rest or during exercise *does exist However in the presence of abnormal chest mechanics due either* to marked pleural fibrosis or to the results of chest surgery, ventilatory insufficiency in these tuberculous subjects may progress to an anoxic phase and then right heart involvement may occur This then is a complicated form of tuberculosis.

In fibrotic and granulomatous diseases which produce cor pulmonale the primary difficulty leading to circulatory complications appears to be an anatomic curtailment of the pulmonary vascular bed which results in pulmonary hypertension It should be emphasized that the fibrotic process must be generalized throughout the lung and located in such a way as to encroach on much of the pulmonary vasculature, either by restricting its expansibility by collar-like perivascular lesions or by actual reduction in the number of the functioning vessels.

Silicosis is one of the more frequently encountered fibrotic diseases associated with cor pulmonale. It has been assumed that these fibrotic lesions induce pulmonary hypertension and then right heart failure Closer inspection has indicated, however, that it is the patient with combined silicosis and emphysema who more usually develops circulatory disease Moreover, we have shown [1] that the circulatory complications can be reversible as the anoxia, which is secondary to emphysema, lessens and this strongly suggests that anatomic lesions may not be the chief offenders and that the emphysema is the root of their difficulties

Although little is known of the circulatory complications in silicosis not associated with emphysema, the picture is a little clearer in that group of rarer diseases which produce lesions in the pulmonary alveolar capillary

membrane. Among these are berylliosis, Boeck's sarcoid, scleroderma, and certain granulomatous lesions and reticular fibroses of undetermined etiology. In these individuals pulmonary hypertension and right heart enlargement may be present before even moderate anoxia appears at rest; therefore, it seems likely that anatomic lesions are primarily responsible for this type of cor pulmonale. Undoubtedly, as the disease progresses and severe anoxia appears, its effects are superimposed If anoxia becomes severe these subjects will even develop polycythemia.

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## DISCUSSION

CHAIRMAN WERKÖ Thank you, Dr. Ferrer, for this most complete discussion of a difficult subject

I would like to put one question before you I noted in the comparison of different groups of emphysema patients you had a cardiac index of 3 15 in the normal and 3 57 or 3 60 in some of the emphysematous patients Do you think this difference is a real one? Is there a statistically significant difference between those two groups?

FERRER We did not have a sufficiently large group of patients to subject them to the stringencies of statistics However, this group had acted as an indication to us, early in our work, that the progressive changes in the emphysematous patient moving toward cardiac failure include a movement of increase in output before the failing state occurred, and at the time these data were secured we did not have the data we showed today in individual *patients at different* stages in their disease. So, while I agree the actual levels of output are only 15 per cent higher in the emphysematous subjects (not a great increase) we thought it indicated a trend

SPAIN I am in complete agreement with you, Dr Ferrer, about the relative importance of structural changes of pulmonary vessels There was one point I noted, however, you said that these patients were free of coronary atherosclerosis.

I would assume that most of these were males, between the ages 45 and 55 It would be a very unusual situation if at least half of them did not have significant coronary atherosclerosis, which at least would subclinically affect the myocardium

Would not this then have an additional effect on myocardial function that you could not measure or be aware of I can't assume that cor pulmonale and coronary atherosclerosis are mutually exclusive. You said all of these cases were free of it I would be quite amazed if this were so.

COURNAND. It would be rather bad taste for me to comment on this presentation, except to indicate some areas of disagreement. Small quarrels are not unknown in our group

I wonder, first, whether Dr Ferrer should not modify her definition of cor pulmonale, so as to introduce also disturbance in the mechanisms of the chest cage, since from such disturbances arise, as she has demonstrated to you, typical cases of alveolar hypoventilation with anoxia, carbon dioxide retention and cardiac failure

Secondly, I am impressed by these cases, in overt congestive failure, showing a satisfactory response to exercise Should we not invoke here the concept of congestive failure, reintroduced recently by Dr Eichna, as distinct from cardiac failure? This may be considered as a problem of semantics In fact, it does not affect Dr Ferrer's concept since, according to it, right ventricular failure complicating some forms of chronic pulmonary disease, is preceded by a period of hypervolemia and plethora related to chronic hypoxia

CHAIRMAN WERKO As I will show you tomorrow, we have induced hypervolemia in normal individuals, and then you increase the right ventricular and diastolic pressure up to 12 mm Hg, and they certainly are not failing The only difference between those normal individuals and the patient with cor pulmonale and hypervolemia is that in the normals we don't get a decrease in filling pressure with digitalis that we get in the patients That may be due to the fact that the former constitutes acute changes in hemodynamics and the latter is a chronic one

COURNAND I have a last statement to make, in order to avoid a misunderstanding with Dr Sarnoff We (including Dr Ferrer) admire his work on the ventricular function curves, and believe that in a single case, one moves from one to another of a series of curves The figure shown by Dr Ferrer is obviously a great simplification

CHAIRMAN WERKO I would like to ask Dr Sarnoff to comment on the concept of "ventricular strain" in a patient who increases his output and pulmonary arterial pressure Obviously the right ventricular work must increase quite considerably

SARNOFF I think what we are discussing here is more a matter of taste than fact Where you want to draw the line about whether you are or are not in love is one aspect of this type of thing, only here it is strain that is under discussion

You take a look at the heart's function curve, and you say this is a pretty poopy heart And it is, it doesn't do much at any given filling pressure Soon after digitalis or catechol amine, the heart begins to look better, and pretty soon it shows a steep and high curve, then one says this is a fine heart It might add somewhat to the explicitness of communication between individuals interested in this area if the curve were quantitatively indicated under these circumstances Unhappily, however, the ever present evil of the non-existent zero baseline for the circulation will interfere somewhat with such attempts

FOWLER Dr Ferrer commented on the fact that one certainly observes

clinically that in the patient with cor pulmonale, the episodes of congestive heart failure are often precipitated by pulmonary infection.

In that connection I wonder if she has any information (I am sure she does) on whether the oxygen consumptions in her patients with cor pulmonale and heart failure were normal or in excess of normal, and whether or not she thinks infection played a role in the high cardiac output observed

The other question I wanted to ask She mentioned the role of hypervolemia in increasing cardiac output. I wonder if she has any data on the cardiac output in patients with polycythemia vera.

FERRER. To answer the second question, no, we do not have any data in polycythemia vera It would be most interesting

To reply to your first inquiry, our patients at the time we measured their cardiac output, were not febrile, and while we acknowledge they may have some underlying chronic infection, we were reassured that the calculation of output was not rendered invalid by abnormal levels of oxygen uptake because, although some of the figures lie at the upper edge of normal resting values, they were not excessive

SARNOFF In addition to thanking Dr Cournand for his generous remark I should like to make one other comment Since it is the *effective* filling pressure (transmural ventricular pressure gradient) with which we are concerned, changes in intrapleural pressure may be hurtful in the attempt to construct convincing ventricular function curves in man, a hazard obviated in the opened-chest dog This applies especially to observations before and during exercise when substantial changes in the mean thoracic position may occur I wonder if Dr. Ferrer and Dr Cournand feel that an esophageal balloon, even if it only reflected relative changes, might be a worthwhile addition to their already challenging experimental technique?

# Physiologic Studies of Drugs in Human Pulmonary Hypertension

*By* Noble O. Fowler

In considering the effects of drugs in human pulmonary hypertension it is important to bear in mind the clinical conditions in which pulmonary hypertension may be found, the possible mechanisms of production of such pulmonary hypertension, and the physiologic mechanisms which may be involved in lowering pulmonary arterial blood pressure.

Although a number of drugs have been shown to decrease pulmonary hypertension in man, the effect of these drugs upon resistance to flow through the lung vascular bed is more difficult to evaluate In our consideration of this problem we plan to discuss not only the agents which may lower pulmonary arterial blood pressure but to consider the mechanisms by which this may be achieved.

Studies of the effect of drugs in human pulmonary hypertension are of importance, first of all, from the standpoint of relief of the undesirable effects of pulmonary hypertension, secondly, for the information which may be derived concerning the mechanism of control of pulmonary arterial blood pressure, and, finally, because they may show whether pulmonary hypertension is reversible or irreversible

Reduction in pulmonary artery pressure by drugs can result from decrease in pulmonary flow, decrease in left atrial pressure, and decrease in resistance to flow through the pulmonary vascular bed The mechanisms of decreased flow resistance in the pulmonary vascular bed are complex; some possibilities follow

*Mechanisms of Decreased Flow Resistance*

1. Vascular
    a) Direct
    b) Autonomic
    c) Reflex
    d) Combating Hypoxia or other Agent
2. Increase left atrial pressure
3. Increase pulmonary arterial pressure
4. Increase pulmonary flow
5. Miscellaneous
    a) Decreased Blood Viscosity
    b) Opening of Shunts
    c) Decrease in Length of Flow Channel

Experimental work in animals has indicated that, although increased left atrial pressure and increased pulmonary flow tend to increase pulmonary arterial pressure, at the same time they tend to decrease the resistance of flow to the pulmonary circulation [1] Thus changes in pulmonary arterial pressure may not reflect concomitant changes in pulmonary resistance. Whether or not

the same considerations apply when the pulmonary vessels are previously diseased is not apparent.

The effect of digitalis upon pulmonary hypertension in patients with left ventricular failure has been discussed earlier in this symposium by Dr Ferrer and will not be commented upon further at this time

In 1949 we became interested in the observations of Frisk[2] that the administration of tetraethylammonium in patients with systemic hypertension produced prolonged lowering of pulmonary arterial blood pressure in 3 subjects

Although the pulmonary vascular bed had long been thought not to be subject to independent control, observations that pulmonary arterial pressure occasionally equals or exceeds systemic pressure suggested that there might be a mechanism for control of pulmonary blood pressure separate from that of the systemic arterial pressure It therefore seemed of interest to attempt to evaluate the mechanism of lowering of pulmonary arterial pressure by tetraethylammonium in patients with pulmonary hypertension by simultaneous estimates of pulmonary arterial blood pressure, pulmonary wedge pressure and pulmonary blood flow The limitations of this experimental approach will be commented on later

The effect of tetraethylammonium was studied by Fowler[3] and Scott.[4] A decrease in pulmonary arterial pressure was observed in the majority of the patients studied that had previously existing pulmonary hypertension Pulmonary wedge pressure was unchanged in the study of Fowler and was decreased in 3 of 6 patients in the study of Scott. The effect of hexamethonium in pulmonary hypertension was studied by Wilson,[5] Davies[6] and Sancetta[7] Decrease in pulmonary arterial pressure was found by Wilson,[5] using rather large doses of hexamethonium Changes in systemic pressure and in cardiac output were less striking than changes in pulmonary arterial pressure Davies[6] studied 12 patients with rheumatic heart disease, and found a decrease in pulmonary arterial pressure of 30 to 40 per cent in 5 subjects, with no change in cardiac output Sancetta's study[7] of 15 patients with pulmonary emphysema demonstrated a decrease in pulmonary arterial pressure of the same order as the decrease of cardiac output Sancetta[7] suggested that because of the decreased pulmonary flow, which would tend to increase pulmonary vascular resistance, there was probably a decrease in the resistance to flow through the pulmonary vascular bed Scott[8] studied the effect of pentolinium in doses of 4 to 8 mg in 8 patients with varied causes of pulmonary hypertension A decline in pulmonary arterial pressure was seen in only one patient.

It would appear that the administration of autonomic blocking drugs is followed by a decrease in pulmonary arterial pressure in a significant percentage of patients, which is probably greater than the effect upon pulmonary flow and pulmonary wedge pressure However, the results are difficult to evaluate because of the varied dosage of drugs used, the varied etiology of pulmonary hypertension studied, and the inaccuracies of pulmonary flow measurement by the Fick principle when short acting drugs are employed

The effect of inhalation of 100 per cent oxygen upon pulmonary hypertension has been evaluated by Dressler,[9] by Westcott,[10] by Wilson,[11] and by McGregor [12] Dressler [9] studied 38 subjects, some of whom had mitral stenosis; the others pulmonary tuberculosis A decline in pulmonary arterial pressure was seen in 43 of 52 studies Pulmonary flow and wedge pressures were not measured Westcott [10] studied the effect of 100 per cent oxygen inhalation in 9 subjects, 2 of whom were normal A decrease in pulmonary arterial pressure of 5 mm. or more was seen in 4 of the 7 subjects with pulmonary hypertension Pulmonary flow and wedge pressure were not measured Wilson [11] studied the effect of 100 per cent oxygen inhalation in 10 patients with severe respiratory disease and systemic oxygen saturation of under 75 per cent. Pulmonary arterial pressure fell 5 mm or more in 5 of the 10 subjects In none of the above studies were flow measurements made McGregor [12] studied the effect of 100 per cent oxygen inhalation in 13 subjects with mitral stenosis. Ten showed a decrease of 10 mm Hg or more in pulmonary arterial mean pressure Total pulmonary resistance fell in 10 and was halved in 2

The studies with oxygen in these patients with pulmonary hypertension showed a definite decrease in pressure in some subjects In only a few instances was the fall great or did the pulmonary arterial pressure return to normal or near normal when previously greatly elevated

Dresdale,[13] Rudolph,[14] and Braun [15] studied the effect of tolazoline (Briscoline) upon the pulmonary arterial pressure in patients with pulmonary hypertension Dresdale [13] gave 75 mg of tolazoline intravenously to a few patients with idiopathic pulmonary hypertension and pulmonary emphysema A striking decrease in pulmonary pressure was seen Cardiac output was said to have been increased Pulmonary wedge pressure was not measured Rudolph [14] observed the effect of tolazoline in doses of 10 to 75 mg in 10 patients with congenital heart disease and left-to-right shunts Pulmonary arterial pressure was unchanged in the majority of patients Braun [15] studied the effects of 25 mg. tolazoline in 14 subjects with mitral stenosis A decrease of pulmonary arterial pressure of 4 mm or more was seen in 12 subjects Cardiac output was said to have been increased or unchanged Meriel [16] studied the effect of the sympatholytic drug hydergine, 0 3 to 0 6 mg in 14 subjects with mitral stenosis, essential pulmonary hypertension, or left ventricular failure Pulmonary arterial pressure was strikingly lowered except in patients with left ventricular failure Halmagyi [22] found a decrease of pulmonary arterial systolic pressure and systolic resistance in subjects with mitral stenosis and left ventricular failure following administration of dibenamine, 0 5 to 2 mg per kg body weight

Four of the 5 above studies have shown a striking fall in pulmonary arterial pressure following sympathetic blockade in the majority of subjects with pulmonary hypertension The estimate of pulmonary flow in 2 of the studies must be considered with caution because of the transient effects of the tolazoline which was used

There have been studies of the effects of other drugs in pulmonary hypertension. Following the observations of Cournand [17] that injection of acetyl-

choline into the pulmonary artery reduced pulmonary arterial pressure in normal and in hypoxic normal subjects, Harris[18] studied the effect of a single injection of acetylcholine upon the pulmonary arterial pressure in patients with pulmonary hypertension of various types. A rather striking decrease in pulmonary arterial pressure was found in 18 of 47 patients studied by Harris In the majority of patients studied by Wood[19] fall in pressure was striking but somewhat less than 50 per cent. In the study by Wood, pulmonary vascular resistance was stated to be decreased. However, the duration of the action of the drug employed would cause one to have difficulty in interpreting this measurement. Halmagyi[20] studied the effect of serpasil, 1 mg. injected into the pulmonary circulation, in 12 patients with mitral stenosis and 1 with ventricular septal defect Pulmonary arterial pressure was significantly decreased and changes in cardiac output were less than changes in pulmonary arterial pressure.

The effect of nitrites on pulmonary blood pressure was observed by Johnson[21] and *Halmagyi*[22] Johnson[21] reported a decrease in pulmonary pressure of 20 to 58 per cent in 10 patients with left ventricular failure following sublingual nitroglycerine Halmagyi[22] observed a mean decrease of pulmonary artery systolic pressure of 11 mm Hg in patients with mitral stenosis, and a decrease of 8 mm Hg in patients with left ventricular failure after giving sodium nitrite

In contrast, Aitchison[23] observed an increase in pulmonary arterial mean pressure of 13 to 84 per cent in 10 patients with rheumatic mitral valve disease following injection of 10 to 20 mg. of apresoline Two patients developed pulmonary edema The increase of pressure was attributed to increase of cardiac output, and tachycardia, which presumably necessitated an increase in left atrial pressure *for proper filling of the left ventricle*

Finally, I would like to refer very briefly to a study of the effect of norepinephrine on pulmonary hypertension, currently in progress in collaboration with Dr R. H Franch of Emory University As shown in the following table a study was made of a patient with pulmonary hypertension associated with ventricular septal defect and left-to-right shunt and increased pulmonary flow.

TABLE 1 —*The Effect of Norepinephrine on Pulmonary Hypertension*

| | L S | Age 10 VSD | |
|---|---|---|---|
| | Control | Norepinephrine 0 35 mcg /Kg /min | After Norepinephrine |
| Systemic flow | 3 5 | 3.5 | — |
| Pulmonary flow | 6 3 | 8 7 | — |
| L R Shunt | 2.8 | 2.8 | — |
| FA B P | 84 | 98 | 88 |
| PA B P | 76 | 82 | — |

Animal studies have shown that norepinephrine increased resistance *to flow* in the pulmonary circulation in the experimental animal when an isolated lobe is perfused A study made by us[24] indicated that in man, infusion of

norepinephrine in doses of 0.1 to 0.4 mcg./Kg /min. produced striking increase in resistance to flow in the systemic circulation but that the increase in pulmonary arterial pressure occurring during the infusion of this drug was due predominantly to an increase in pulmonary wedge pressure and was not associated with increase in calculated pulmonary vascular resistance Thus, in the intact subject, pulmonary arterial constricting effect may be masked by a concomitant increase in pulmonary venous pressure. The foregoing suggested the possibility that the differential effect of norepinephrine upon pulmonary and systemic resistances might be anticipated to increase pulmonary flow and left-to-right shunt in patients with ventricular septal defect and pulmonary hypertension In the patient whose study is described on the table, infusion of 0 35 mcg /Kg /min. of norepinephrine was associated with no change in systemic flow, increase in pulmonary flow, and striking increase in left-to-right shunt. Although there was an increase in both femoral and pulmonary arterial mean pressures, the increase in femoral pressure was greater and estimates of pulmonary and systemic vascular resistance would indicate that systemic vascular resistance increased and pulmonary vascular resistance decreased during the norepinephrine infusion

From the foregoing it may be seen that decline in pulmonary arterial pressure has occurred following the administration of autonomic blocking agents, following the administration of sympatholytic agents and following the administration of parasympathomimetic agents Decline in pulmonary artery pressure has also occurred with the use of digitalis in left ventricular failure and to a moderate extent when oxygen was administered. Decline in pulmonary arterial pressure has not been consistent from study to study nor in all patients in a given study. The evaluation of the mechanism by which these changes in pressure occur is difficult.

Some of the difficulties in the evaluation of changes in pulmonary pressure in subjects with pulmonary hypertension are

1 Multiple mechanisms may be present
2 Subjects with various heart and lung diseases often grouped together
3 Limitations of pulmonary wedge pressure
4 Difficulty of determining pulmonary flow by Fick principle
5 Drug may alter more than one variable affecting pulmonary vascular resistance
6 ?—Completeness of autonomic blockade

There is at least suggestive evidence that not all changes in pulmonary pressure are related to alterations in pulmonary flow. However, the transient nature of the changes following use of such drugs as tetraethylammonium, priscoline, acetylcholine would tend to mitigate the evaluation of pulmonary flow by the Fick principle In many instances no estimation of left atrial pressure by the pulmonary wedging technique has been made in human studies and the validity of this measurement is still open to question A recent paper by Murphy [25] indicated little or no correlation between left atrial and pulmonary wedge pressure in patients with mitral valve disease when the left atrial pressure was abnormally elevated It would seem that there is a need for further studies in which a steady state can be achieved so that the Fick

principle can be employed for evaluation of pulmonary flow or some other method of measurement should be used. The results thus far would appear to suggest that in some instances drug induced blockade of the sympathetic nervous system or stimulation of the parasympathetic nervous system may actually decrease the resistance to flow in the pulmonary circulation.

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## DISCUSSION

BLOUNT I have one slide that I should like to show (fig 1) Dr Grover has been interested in the effect of priscoline in young children with ventricular septal defects, who have very significant pulmonary hypertension but who do have some left to right shunt This study was in a thirteen month old infant *One mg of priscoline per kg of body weight was injected into the catheter* placed in the pulmonary artery Four minutes after the injection, we see, on the right of the slide that the femoral artery pressure has changed very little, but that a definite drop in pulmonary arterial pressure has occurred This drop in pressure occurred at the same time that there was a doubling of the pulmonary artery blood flow

Of course, I am hesitant to make any statements about resistance, but it does seem that *with this drop in pressure and the doubling of* the flow, that we possibly might suggest that there is some change in resistance

DAWES: It seems that we now have a good measure of agreement that inflation of the lungs with a low oxygen mixture or with nitrogen causes an

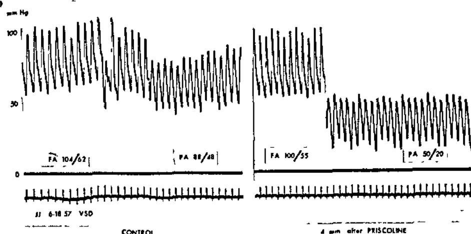



Fig 1—Effect of priscoline on femoral (FA) and pulmonary arterial (PA) pressures.

increase of pulmonary vascular resistance. I have two simple questions to ask about this Duke and Killick have shown that injection of cyanide or azide causes a fall of pulmonary vascular resistance in isolated cats' lungs; these substances should interfere with the use of oxygen by the enzymes in the pulmonary vessels

How then is it that inflation of the lungs with low oxygen mixtures causes a *rise* in pulmonary vascular resistance while injection of azide or cyanide causes a *fall?*

KATZ. In regard to Dr Dawes' question, Dr Carmen Estrada, Dr Singer and several others of our group have reported in the January issue of *Circulation Research* an experiment in the dog in which 5 per cent oxygen and 95 per cent nitrogen were used in the inspired air and left atrial, pulmonary arterial wedge and pulmonary arterial pressures were measured The findings were that in some of these dogs the left atrial pressure did not rise with this severe degree of hypoxia and yet the pulmonary arterial pressure rose In most, but not all, the pulmonary arterial wedge pressure rose more This is in the dog anesthetized with barbiturate, not in man In dogs pulmonary arterial wedge pressure does not necessarily follow left atrial pressure Now, by getting the pressure gradient it was found that in these animals the gradient from the pulmonary arterial wedge to the left atrium rose with hypoxia, suggesting to us the possibility that there was venomotor constriction This is a suggestion, not a proven fact

At the same time the pulmonary artery to pulmonary arterial wedge pressure rose less and in some instances declined suggesting to us the possibility that in the pulmonary system, as in the systemic, there is on occasion truly an arteriolar dilatation When it occurs it is apparently compensated for in these dogs by a more profound venomotor stricture However, we have seen in some of these animals a combination suggesting arteriolar as well as venu-

lar constriction during hypoxia which act in series to raise pulmonary arterial pressure.

DAWES: I wonder if you have done similar experiments on isolated perfused dog lungs?

KATZ: No, we have not.

FISHMAN: In a recent issue of *Circulation Research*, members of Dr. Katz's laboratory, have suggested that pulmonary venoconstriction may underlie the pulmonary pressor response to acute hypoxia. The conclusions are based on a blood pressure gradient between the pulmonary veins and the left atrium during acute hypoxia. Unfortunately, the evidence is not entirely convincing because of its heavy dependence upon pulmonary "wedge" pressure as a measure of pulmonary venous pressure: the actual tracings are not reproduced, the possibility of an inadequate "wedging" is not excluded, the identity of "wedge" and venous pressure is implied, and a sphincteric mechanism between the pulmonary veins and the left atrium is inferred. Before accepting the pulmonary veins as the locus of increased resistance during acute hypoxia, I would prefer more direct measurements.

This paper also illustrates the difficulties which have beset all who have attempted to analyze the mechanisms involved in the pulmonary pressor response to acute hypoxia. Thus, attempts to work with carefully controlled, artificial preparations often yield results which are characteristic only of the *abnormal preparations under study*. *Other experiments performed on more* intact but deeply anesthetized animals, have to reconcile data so obtained with results on unanesthetized animals and man. Finally, even the physiological significance of data collected on unanesthetized human subjects may be difficult to interpret since the majority of observations have been made on patients with disease and have to be extrapolated to normal human subjects.

If I may confine my remaining remarks to the unanesthetized normal human subject, I should like to indicate the few glimpses of insight which have been gained. For example, it seems clear that an increase in cardiac output, generally of the order of 10 to 20 per cent above control, contributes to, but does not account for, the entire pressor response. Moreover, there is considerable evidence than an increase in pulmonary vascular resistance to blood flow is also involved. But, how this increase is effected or what brings it about is not well understood. Certain mechanisms, such as a reflex increase in vasomotor activity mediated from afar by the sympathetic nervous system, or an increase in pulmonary blood volume do not seem to be responsible. Others, such as an increase in left atrial pressure have not been tested in man, but, on the basis of "wedge" pressures, do not seem likely.

Finally, although teleology tempts us to invoke a *local*, self-regulatory vasoconstriction of the pulmonary blood vessels to hypoxia, it must be admitted that the inaccessibility of the pulmonary circulation has defeated attempts to either define an exact site of increased vascular resistance or to distinguish between vascular and peri-vascular responses.

CHAIRMAN WERKÖ: In human beings, hypoxia does not increase the wedge pressure while it increases the pulmonary artery pressure.

COURNAND: I should like to compliment Dr. Fowler on his excellent review and cautious conclusion Possibly even greater caution is warranted when one compiles the results of studies made by many investigators, some of them having only a faint notion of what control studies mean, and in patients with considerable variation in pulmonary vascular lesions.

May I comment on quinidine. You may recall that Drs Ferrer and Harvey [1] observed, to their surprise, that in a patient with mitral stenosis the pulmonary arterial pressure dropped following administration of quinidine sulfate in therapeutic dosage. We know, however, that this drug has a dilator effect upon the systemic arteries. It was therefore concluded that the reduction in pulmonary artery pressure, in such a case, was secondary to a decrease in left heart filling pressure resulting from the decrease in peripheral vascular resistance

With regard to the role of the autonomic nervous system in controlling pulmonary vasomotricity, the problem is not whether there is a supply of autonomic nerves to the pulmonary vascular bed, or whether in special preparations, under artificial conditions, responses may be elicited which indicate the participation of this supply; rather, it is whether in intact man or animal, under normal physiologic conditions, or in disease, this system plays a role in the control of the pulmonary circulation Incidentally, had de Burgh Daly read carefully what I wrote in 1947 on this subject,[2] he might not have accused me, in a recent review on this subject [3] of denying such role to the autonomic system on the basis of an *a priori* idea I do not mind too much this qualification since hypothesis and concepts are an integral part of scientific thinking However, I object to the implication that observed facts are foreign to my thinking

In this respect, may I recall firstly that little attention has been paid to the effects of sympathectomy upon the pulmonary circulation in subjects with malignant hypertension In *1943–1944*, in collaboration with Drs Goldring and Chasis, we studied the pulmonary blood flow, the systolic and diastolic pressure in the right ventricle, and the systemic blood pressure in five patients with malignant hypertension before and after total sympathectomy In these cases, the systolic pressures in the right ventricle were normal before, and remained unaltered after surgery, although the systemic pressures dropped markedly

Secondly, with Alfred P Fishman and Harry Fritts,[4] we have studied so far, two cases before and after sympathectomy in whom the effect of hypoxia in causing pulmonary hypertension was unaffected In other studies upon the effect of acetylcholine injected in one of the two main branches of the pulmonary artery,[5] we have observed homolateral increase in flow in atropinized subjects For these reasons and others also, I believe that the problem of local vasomotor action in man may be divorced from that of the nervous control of pulmonary vasomotricity

FOWLER I would agree with the previous speakers that in our hands there was no elevation of pulmonary wedge pressure in hypoxia Of course, I want

to point out that the degree of hypoxia induced by us and in most studies in man did not approach that produced by Dr. Katz in his dogs

The other comment is in regard to pulmonary arterial pressure in sympathectomized patients I think it might be interesting to see if the patients had normal pulmonary pressure when they were standing up We have done some studies in patients under autonomic blockade that were interesting,—they had a normal pulmonary arterial pressure lying down; when they sat up the pressure became very low, and the cardiac output fell as well.

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# V. THE PULMONARY CIRCULATION IN CONCENITAL HEART DISEASE

CHAIRMAN: HOWARD B. BURCHELL
CO-CHAIRMAN: BENJAMIN M. GASUL

## The Pulmonary Circulation After Birth

*By* GEOFFREY S DAWES

IT HAS BEEN REPORTED that nowadays more children die of natural causes in the first 7 days of life than in the next 14 years Since many of these deaths are due to diseases involving the pulmonary circulation, it is important that we concern ourselves with the changes which occur at birth

The investigation of the changes in the lungs at birth are best begun with a study of the pulmonary circulation in the fetus In the anesthetized foetal lamb indirect calculations suggest that 12 per cent of the combined output of both ventricles passes through the lungs, amounting to about 30 ml /Kg /min (Dawes, Mott & Widdicombe, *1951;* Acheson, Dawes & Mott, *1957*) This agrees moderately well with direct measurements of flow through the left lung, which range from 5 to 10 ml /Kg /min In the anesthetized newborn lamb venous return to the right side of the heart is about 300 ml /Kg /min There is therefore a very great change in pulmonary blood flow at birth; previous measurements have underestimated the magnitude of this change The cause of the increase in pulmonary blood flow is *unquestionably a fall in* pulmonary vascular resistance, since it is accompanied by a considerable reduction in pulmonary arterial pressure and a small, although probably transient, rise in left atrial pressure (Dawes, Mott, Widdicombe & Wyatt, *1953*) Whereas in the fetus pulmonary arterial pressure exceeds aortic pressure by a few mm Hg (so that two-thirds or more of the right ventricular output flows through the ductus arteriosus into the aorta), after birth pulmonary arterial pressure rapidly falls towards adult levels Thus in the foetal lamb the pressure in the pulmonary trunk may be 65 mm Hg On ventilation it can fall to 20 mm Hg within a few minutes We must now consider the cause and the effects of these dramatic events

Positive pressure ventilation of the lungs of foetal lambs with either oxygen, air or nitrogen caused a large and immediate fall in pulmonary vascular resistance, whereas distension with fluid actually increased resistance This demonstrates that it is not the fall of intrathoracic pressure which increases pulmo-

nary blood flow at birth, but expansion of the lungs with a gas. This distension does not need to be rhythmical, since a single sudden inflation, even with nitrogen, has on occasion caused a sudden fourfold increase in flow. It seems possible, therefore, as Reynolds (*1956*) has suggested, that this phenomenon is due to a simple anatomical feature of the lung vessels, perhaps the uncoiling and dilatation of the alveolar capillaries, which in the foetal condition may be convoluted and compressed. Pulmonary collapse in adults does not necessarily lead to cyanosis, because as ventilation is decreased, so flow is also reduced through the affected area. This may be another illustration of the same phenomenon

There are other minor factors which probably influence pulmonary vascular resistance at birth, such as the oxygen content of the alveolar gas, vasomotor changes due to asphyxia and the rise in left atrial pressure which also occurs. However, these are likely to be very much less important than the immediate physical effect of pulmonary inflation We must now examine the consequences of the fall in pulmonary vascular resistance in more detail

Since pulmonary arterial pressure falls below aortic pressure after birth, the direction of blood flow through the ductus arteriosus reverses As the ductus does not immediately close and as it is a very short vessel, a very large quantity of blood, amounting to as much as half the total pulmonary blood flow, enters the pulmonary trunk from the ductus The ductus normally begins to constrict within some minutes of birth, particularly in the presence of partial asphyxia, though this process is not usually complete for many hours or days in the species so far examined. Rapid blood flow through the partly constricted ductus gives rise to turbulent flow, and hence to a murmur which can be heard through the chest wall and sometimes even to a thrill This ductus murmur is very easy to hear in the newborn lamb, calf and foal (Dawes, Mott & Widdicombe, *1955;* Amoroso, Dawes, & Mott, *1958;* Rossdale & Mahaffey, *1958*) and may persist for as long as two days If the chest is opened under anesthesia, the vibrations of the pulmonary trunk are readily felt, and can be recorded with a manometer When the ductus is occluded, this murmur disappears

In the newborn baby recent investigations have shown that the same changes occur A murmur can be heard, although it is fainter, and much more difficult to record, possibly because of the different shape of the infant's chest, and the lower blood pressure (Burnard, *1958*) Measurements of pulmonary and systemic arterial pressures, and of the oxygen content of blood obtained from the right ventricle and pulmonary artery by catheterization, have proved that for as much as 10 days after birth blood may enter the pulmonary trunk from the aorta (James & Rowe, *1957;* Adams & Lind, *1957*)

The consequences of this neonatal condition of the circulation are fourfold *First*, as in children or adults, patency of the ductus arteriosus after birth unquestionably throws a greater strain upon the left side of the heart. There is therefore the possibility of left-sided heart failure within a few days of birth. *Second*, against this has to be set a temporary advantage When the lung is not yet fully expanded, the unexpanded portions act as an intra-

pulmonary arterio-venous shunt across the lungs, so that for up to an hour after birth the arterial blood is not fully saturated with oxygen. Continued patency of the ductus enables some of this blood to recirculate through the lungs, and thereby to pick up more oxygen (Dawes, Mott & Widdicombe, *1955;* Born, Dawes & Mott, *1955*). If a newborn animal is badly cyanotic the benefit can be surprisingly large, and occlusion of the ductus under such circumstances leads to a considerable fall in arterial oxygen saturation *Third,* there is always the possibility that so long as the ductus is still open, the direction of flow may revert to the foetal condition When a newborn animal or baby makes a strong expiratory effort, for instance, pulmonary arterial blood may enter the aorta through the ductus, and the oxygen content of blood in the descending aorta will then become less than that in the coronary or carotid arteries If a newborn lamb or baby is underventilated, or given a gas mixture to breathe which only contains 15 or 10 per cent $O_2$, pulmonary vascular resistance increases, just as it does in adults, and blood starts to flow once more in the foetal direction, from the pulmonary trunk into the aorta To what extent this situation represents a hazard to the survival of asphyxiated newborn babies or animals is not known *Fourth,* it is perhaps worth making the very obvious point that while the ductus is patent, systemic arterial pressure will be lower and pulmonary arterial pressure higher than when it is shut

That is, I hope, enough to introduce this subject I would like to conclude with some words of Edmund Waller, which epitomize the hopes and fears of every investigator of the pulmonary circulation

My joy, my grief, my hope, my love
do all within this circle move
A narrow compass, and yet there
dwells all that's good, and all that's fair

Nicely put, written in Harvey's time, but what Waller really had so delicately in mind was not, alas, the circulation through the lungs, but a lady's girdle

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## DISCUSSION

ROWE Dr Dawes' work has been a major stimulus to those working in this area in humans and he made the job rather easy by predicting what would be found on catheterization of newborn babies

The results in the group we analyzed showed that the pulmonary arterial pressure in those less than a week old averaged 50/25, with a mean of 35 mm Hg, and in that group there was a large shunt through the ductus arteriosus which amounted to about a third of the pulmonary blood flow.

At the end of a week, the pulmonary arterial pressure averages 22/11, with a mean of 16, and no ductal shunt is detected We do not know exactly when the duct closes

Newborn infants do not have the continuous murmur which Dr. Dawes found in animals During the first few hours of life they exhibit physical signs strongly suggestive of pulmonary hypertension There is a very loud, but not split, second sound in the pulmonic area. There is a pulmonary ejection click.

It is quite possible, however, that a murmur appears later Electrocardiographic evidence suggests that this murmur might appear when the infant is between 24 and 96 hours old.

DAMMANN. In the work that you have done, Dr Dawes, the remarkable shift in pulmonary resistance that occurs right after birth is equated with the first few respirations You have demonstrated that if the lung is distended with saline, a drop in pulmonary resistance does not occur whereas, if the lung is distended with a gas, such as nitrogen, oxygen, or carbon dioxide, there is a remarkable drop in pulmonary resistance. Does this not suggest that the drop in pulmonary resistance is related to the shift from a relatively noncompressible fluid to an easily compressible gas filling the alveolar spaces?

DAWES I do not know the answer If you instill warm saline into the lung you do *not* get an increase in pulmonary blood flow In the fetus you actually get an increase in pulmonary vascular resistance in the majority of experiments It may be that the lung is more complicated than we have hitherto supposed and that in distending the alveoli with saline we had compressed the alveolar capillaries When the alveoli are distended with air, we have a totally different physical situation I do not know of any experimental evidence which can be adduced to support this hypothesis

BURTON. May I speak briefly to this point? I would like to call your attention to a most remarkable recent paper by Dr Radford

He examined the compliance of excised lungs, and after measuring the pressure-volume relations, he repeated the examination with the lungs filled with saline instead of air To everyone's astonishment the compliance was completely different, the answer being that actually a lot of what we call elasticity in the lungs is really surface tension, tending to make the alveoli get smaller If you increase the surface area you have to supply the energy for this additional surface energy So, the substitution of air for fluid might well be a factor in what Dr Dawes is talking about

DEXTER I would like to ask Dr Dawes a very simple-minded question If you should give these newborn infants a hot bath, thereby producing peripheral vasodilatation and lowering of peripheral resistance, would their murmur disappear?

DAWES. Dr Burnard observed that those babies which suffered from a short

period of, say, 5 minutes difficulty in breathing at birth had a higher incidence of murmurs He also heard murmurs more often in infants with high rectal temperatures

This may not answer your question but it does point up the fact that other physiological changes in the infant are extremely important, and it may be these differences which explain the discrepancy between Burnard's observations and those of Dr Rowe and others

WOOD Dr. Dawes, I wonder if you are right in assuming that air, oxygen or gas fully distends the neonatal lung or that saline does so You might have to stretch the lung fully to get rid of those "gnarled" vessels I thought that a lung needed to be vascularized in order to be distended and stretched, that the pulmonary blood flow after birth was an essential factor in stretching and inflating the lung Is that work no longer respected?

DAWES · You are referring, I suppose to Dr Jakka's observations, and his observations were made on a rather unusual kind of material I don't think that the inferences that he drew from his observations were really justified, because, when you inflate a lung for the first time, the first thing that you notice is a fall in pulmonary artery pressure and an increase in flow I cannot see how a rise in pulmonary arterial pressure can help in the distension of the lung

WOOD I am still not happy about this Surely it is not exactly a matter of pressure There is very little blood flowing through the fetal lung and the vessels are all there and presumably coiled up

If you suddenly increase the pulmonary blood flow, irrespective of inflating the lung with gas, would not those vessels stretch, as was demonstrated in the work that we are talking about? I thought that you could not fully inflate a lung with anything until you got a proper blood flow

DAWES In order to inflate the lungs of a newborn animal effectively, you have to use a positive pressure of 30 to 40 mm Hg This is not an abnormal pressure for the newborn

If you take an animal delivered under local anesthesia, when you tie the cord so that the lamb starts breathing, the intrapleural pressure during the first few gasps falls as low as minus 50 mm Hg It is this effort which first inflates the lung Thereafter pulmonary blood flow increases

WOOD If you tie off both arteries, can you still inflate the lung completely?

DAWES We have not done that

DAMMANN May I make a suggestion? The lung and pulmonary vascular bed is expanded by an increase in effective trans-luminal pressure Such an increase can be brought about either by increasing intraluminal pressure or by decreasing extravascular pressure The decrease in extravascular pressure is normally brought about by the shift from fluid to air in the alveolar spaces

# The Pulmonary Circulation in the Presence of Interatrial, Interventricular and Interarterial Communications

*By* John T. Shepherd

Two basic measurements that are essential to any understanding of the dynamics of the pulmonary circulation are pressure and flow. Two terms that employ these measurements are now used frequently The first, the total pulmonary resistance, is essentially the ratio of the mean pressure in the pulmonary artery to the mean pulmonary blood flow, and the second, the pulmonary arteriolar resistance or, better, the pulmonary vascular resistance, is the ratio of the pulmonary-artery pressure minus the left atrial pressure to the mean pulmonary flow

The first of these terms attempts to define the resistance offered to the flow of blood from the right to the left ventricle and includes the work done in distending the left ventricle in diastole, the second defines the resistance offered by the blood vessels of the lungs themselves. The finding of increased resistance means that the observed increase in pulmonary arterial pressure is disproportionately greater than the increase in pulmonary blood flow. In normal subjects the resistance to flow usually diminishes as flow increases, demonstrating that the flow has increased proportionately more than the pressure [1,2] If pressure and flow increase equally, one is dealing essentially with a rigid tube-like system, and if pressure rises more than flow, then a decrease in vessel caliber can be assumed It must be emphasized, however, that deductions about changes in vessel caliber from these formulas are based on the Poiseuille equation in which resistance is proportional to pressure gradient divided by rate of blood flow [3] Theoretically, the use of this formula as a measure of resistance is based on the assumption, among others, that there are a nonpulsatile pressure gradient and a steady flow As neither of these conditions is fulfilled in the pulmonary circulation, prediction of changes in vessel caliber from resistance values obtained in this way must be accepted with reservation

## Evidence for Pulmonary Vasomotor Tone in Patients With Congenital Heart Disease

While in many patients with atrial, ventricular or aorticopulmonary communication the total pulmonary resistance and the pulmonary vascular resistance are within normal limits, in others the total pulmonary resistance is markedly elevated [4] As most of these patients have a normal "wedge" pressure, and hence presumably a normal left atrial pressure,[5,6] the site of the increased resistance to flow is the pulmonary vascular bed Although, when

normal, the vessels responsible for pulmonary resistance have relatively little smooth muscle as compared with similar vessels in the systemic circulation, there is convincing evidence from the effects of hypoxia,[7,10] and more recently from the effects of 5-hydroxytryptamine,[11] that they are capable of constriction. Among certain patients with congenital defects the likelihood that some of those who have pulmonary hypertension have maintained their fetal pulmonary vascular musculature into postnatal life[12] presumably makes these pulmonary vessels even more capable of vasomotor responses. That tone is present in the smooth muscle of the pulmonary vessels in some patients with defects in the heart and great vessels can be demonstrated by two different methods. First, a change from breathing air to breathing 99 per cent oxygen is accompanied in many of these patients by a fall in total pulmonary resistance and in pulmonary vascular resistance, often by more than a third of the initial values.[13-17] This effect of oxygen is accompanied by a fall of pressure in the pulmonary artery and an augmentation of the left-to-right shunt with a diminution of any right-to-left shunt that may be present. This change in resistance appears to be quite independent of the type of defect. The method by which it occurs is unknown.

Second, acetylcholine chloride, a substance which when injected intra-arterially into systemic vessels causes local vasodilatation,[18] has recently been used in the study of the pulmonary circulation. Its rapid destruction in the circulating blood offers the possibility that an injection can be made into the pulmonary artery in sufficient concentration to affect the pulmonary vessels without altering the hemodynamics on the left side of the heart or in the systemic circulation. Wood and co-workers[19] have used a single injection of this substance and have shown that tone is present in the resistance vessels of the lungs in some patients with mitral stenosis. Harris[20] found that rapid injections into the pulmonary artery of patients with pulmonary hypertension, some of whom had congenital heart disease, resulted in a transient fall of pressure in the pulmonary artery in slightly more than one-third of the patients. We have administered acetylcholine chloride by continuous infusion into the pulmonary artery in patients with congenital heart disease. Figure 1

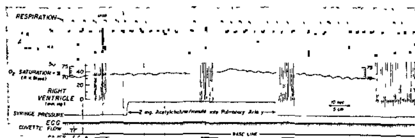



FIG 1.—Effect of continuous infusion of acetylcholine chloride into the pulmonary artery on pressure in the right ventricle and the radial artery and on the oxygen saturation of blood in the right ventricular outflow tract. Woman, aged 45 years, weighing 63.2 Kg., with atrial septal defect and pulmonary flow of 3.7 L./min./M.²

shows the effects of such an infusion in a patient with pulmonary hypertension associated with an atrial septal defect. During the infusion there were a marked decrease in systolic pressure in the right ventricle and an increase in the oxygen saturation of the blood in the pulmonary artery. In the absence of any change in systemic blood pressure, oxygen consumption or heart rate, one must conclude that the acetylcholine has dilated the pulmonary vessels with a consequent decreased resistance to pulmonary flow and an augmentation of the left-to-right shunt

It therefore seems clear that the tone of the small vessels of the lungs contributes to the pulmonary hypertension in patients with congenital heart disease who have an abnormal communication between the heart chambers or the great vessels.

## Factors Associated With Development of Pulmonary Hypertension

### *Ventricular Septal Defect and Patent Ductus Arteriosus*

In patients with an interventricular communication, there must be a critical size for the defect above which the pressures in the right and left ventricles will equalize, while defects less than this will offer sufficient impedance to blood flow between the ventricles to prevent equalization of pressures The amount of blood that passes through the defect will depend, therefore, on the resistance offered by the defect itself and the resistances of the pulmonary and systemic circulations Clearly, when the defect is of more than a certain size, there will be very little resistance to flow across it, hence the amount of blood that enters the pulmonary as compared to the systemic circulation is a function of the relative resistance of these two circuits This is demonstrated by recent observations made in this laboratory where pulmonary and systemic blood flows and pressures have been determined at cardiac catheterization and correlated with the size of the ventricular septal defect as measured at operation[21] A defect greater in area than 1 sq cm./$M^2$ of body surface offers so little resistance to flow across it that the pressure is equalized in the two ventricles If no change in pulmonary resistance occurred in these cases, death would rapidly supervene from ventricular failure and hypotension, as nearly all the blood would pass through the low resistance pulmonary circuit This occurs in adult dogs when an interventricular defect greater than 1 cm in diameter is created[22]

In man, when the size of the defect exceeds 1 sq cm /$M^2$ of body surface the magnitude of the pulmonary flow is determined mainly by the response of the pulmonary vessels. These vessels usually offer an increased resistance to flow which, depending on its extent, can result in a whole spectrum of change from a high pulmonary-artery pressure with a large flow and a moderate increase in resistance to a high pulmonary-artery pressure, a low flow and a very high pulmonary vascular resistance When pulmonary blood flow and total pulmonary resistance are plotted against the systolic pres-

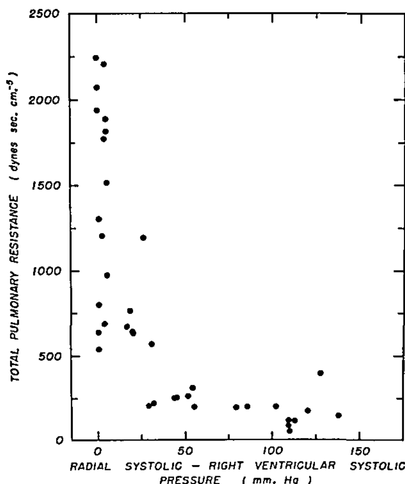



FIG 2 —Relationship between total pulmonary resistance and systolic pressure gradient across a ventricular septal defect

sure gradient across the ventricular septal defect (fig 2), patients with a large gradient have a normal resistance and a near-normal flow As the gradient decreases, there is a marked increase in flow with a small increase in resistance As the gradient approaches zero, the flow often decreases markedly and the resistance is usually greatly increased

In patent ductus arteriosus the circulatory dynamics are very similar to those in ventricular septal defect Across a long narrow ductus there is a drop in pressure With a larger ductus the drop in pressure decreases and the pulmonary flow increases with little change in pulmonary resistance When the ductus is short and wide, the pulmonary and systemic circuits are essentially in free communication and the flow through the pulmonary and systemic circuits is then determined by their relative resistances Under these conditions, the pulmonary flow is often decreased, the pressure in the pulmonary artery approaches or equals systemic pressure, and the pulmonary vascular

resistance is very high. Thus a short wide ductus and a large ventricular septal defect are *nonobstructive openings permitting free communication* between pulmonary and systemic circuits so that the pressures in the aorta and the pulmonary artery are equivalent

*Atrial Septal Defect*

In this condition the two atria form essentially a common chamber, and the basis for the arteriovenous shunt commonly seen in patients with this defect is that during diastole more blood flows into the right ventricle than the left because of the lower resistance to filling. This situation is markedly different from that of ventricular septal defect or patent ductus arteriosus, as at no time is the right side of the heart exposed to a high pressure generated initially in the left ventricle. The hemodynamics in the classic case of atrial septal defect are well documented[23] Pressure in the pulmonary artery is normal or only slightly elevated, the pulmonary flow is moderately to excessively increased and the pulmonary resistance is low, some of these patients, however, especially those reaching the fourth decade of life, develop an increased pulmonary vascular resistance which is progressive.[24] This is different from the situation in patients with ventricular septal defect or patent ductus who have little decrement of pressure across the defect; in such patients the ratio of pulmonary to systemic vascular resistance appears to increase with age starting from shortly after birth[25] That is to say, if the pulmonary vessels are not protected by a drop in pressure across the intraventricular defect or the patent ductus, not only is the pulmonary vascular resistance increased but this increase may be progressive

## Mechanism for Maintenance of Tone of Smooth Muscle of Pulmonary Vessels

Pulmonary hypertension is a frequent finding in patients with ventricular septal defect and aorticopulmonary communication, and although less often seen in patients with atrial septal defect, it is by no means uncommon High pulmonary blood flows induced in normal subjects by moderate exercise or occurring in conjunction with a typical atrial septal defect are usually accompanied by a decrease in pulmonary vascular resistance While part of this may possibly be accounted for by opening up previously closed vessels, it is likely that at least some of it is due to an increase in diameter of vessels already open The mechanism of this is unknown, but it is possible that dilation of the vessels is brought about passively, the increase in flow increasing the vascular transmural pressure If pulmonary vessels can increase their caliber in this way, why does a marked rise of pressure in the pulmonary artery occur in patients with ventricular septal defect and aorticopulmonary communication when the defect itself offers no appreciable resistance to flow? Has the large flow generated by the transference of the systemic pressure to the pulmonary circuit so distended the vessels that they have reached their limits of dilation? This seems unlikely, as creation of large defects of this kind in adult dogs does not cause severe hypertension but leads to rapid death of the animal by a

failure of the pulmonary vessels to constrict and so reduce the pulmonary flow.[22]

Recent observations indicate that tone is present to some degree in normal pulmonary vessels,[26 27] although the contribution of this compared to mechanical factors in determining pressure in the pulmonary artery is undecided Evidence that many patients with pulmonary hypertension have tone in the smooth muscle of the pulmonary vessels has already been cited, and this tone, at least in part, contributes to the hypertension This is true even for patients in whom the hypertension is classified as hyperkinetic An increase in tone means that the wall of the vessel is actively resisting the distending force tending to dilate it. The effect of this on the caliber of the vessel will depend on the sum of these two forces The caliber may thus be increased, unchanged or decreased. Whether the degree of tone is to be regarded as normal or abnormal in pulmonary hypertension cannot yet be stated with certainty, as the relative contribution of this and histopathologic changes in the vessels to the increased vascular resistance is unknown

What is the stimulus that maintains this tone of the vessels? The argument can be advanced that increased pressure is a common finding in all cases, but it is difficult to dissociate cause and effect Two sets of observations obtained from patients with acquired heart disease are compatible with the concept that changes in pressure can cause changes in the tone of smooth muscle If the pulmonary vascular resistance is measured in a series of patients with mitral stenosis, both at rest and during exercise, those in whom the resistance is low at rest show little change with exercise, whereas those in whom it is initially high often show a substantial increase Further, in some of those in whom a substantial increase occurs, there is little change in cardiac output [28] Similar observations have been reported by Eliasch [29] and by Holling and Venner [30] If the simple equation relating pressure and flow is an indication of changes in the caliber of the vessel, this finding is compatible with the idea that increase in pressure and not flow was the stimulus to the smooth muscle, although one could not say whether it was the general rise in pressure or the rise in pulmonary venous pressure which was responsible Balchum and co-workers [31] have suggested that this change in pulmonary vascular resistance with exercise is not mediated by nerves since the change before hexamethonium block is approximately equal to the change after such block Further, if a group of such patients are examined before and within 2 to 5 weeks of mitral commissurotomy, those that have the highest pulmonary arteriolar resistance before operation have the greatest decrease afterward [32] This is in keeping with the idea that the reduction in pressure somewhere in the pulmonary circuit has permitted a relaxation of tone in the walls of the resistance vessels, and if this is correct then the tone has probably been abnormal in degree The early decrease in resistance after operation makes it likely that it is a vasomotor phenomenon rather than the regression of pathologic changes

If this argument were applied to pulmonary hypertension in congenital heart disease, one might theorize that with a large ventricular septal defect or a short wide ductus the high pressure of the ventricles is transmitted to

the pulmonary vessels, and it could be that this pressure causes persistence of the fetal muscle typical of these two conditions and that this muscle responds to the pressure by augmentation of its tone[33] In the systemic circulation it has been shown in animals and man that the resistance vessels respond to a rise in pressure by increasing their tone.[34 37] This still occurs after the limbs have been sympathectomized or somatically denervated.[38] It is improbable, therefore, that any nervous mechanism is involved, and the results can be readily explained on the basis of a direct response to the mechanical stimulus of the muscle elements of the resistance vessels by the increased pressure.

Such an argument when applied to the congenital defect leaves unexplained the etiology of the hypertension in some patients with atrial septal defect Other theories have been advanced to support a nervous[38 40] or even a humoral[11] cause of the hypertension In a recent review article by Daly,[41] evidence is presented that in the dog the upper thoracic sympathetic outflow contains adrenergic vasoconstrictor fibers to the pulmonary vascular bed which when stimulated can increase the pulmonary vascular resistance by 60 per cent or more Daily also reviews the evidence for active pulmonary vasomotor control in man and concludes that none of the observations in human subjects so far reported fulfills all the criteria that are essential for the demonstration of an active control.

## Summary

The evidence reviewed here demonstrates that tone is present in the pulmonary vessels in many patients with pulmonary hypertension The argument is advanced that a rise in transmural pressure somewhere in the pulmonary circulation or left atrium is a major factor in initiating and maintaining the increased pulmonary vascular resistance in such patients The rise in pressure may result in increased tone of the pulmonary vessels either via a nervous reflex or through a local response of the smooth muscle to the rise in pressure

## Acknowledgement

I wish to thank Drs H B Burchell, H W Marshall, R M. Savard, H. J Semler, H J C Swan and E H Wood for making readily available to me from their own studies many of the data for this talk. I am especially indebted to Drs Swan and Wood for their advice and criticism and for reviewing their data with me

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## DISCUSSION

GASUL We have been very much interested in a follow-up study of patients with ventricular septal defects About two years ago in re-examining some of our infants with this defect we found something that may be of interest A patient (J M) 11 months of age presented all the clinical, radiologic and electrocardiographic evidences of a large ventricular septal defect He had a loud second sound over the pulmonary area, a thrill and a harsh grade IV systolic murmur maximal over the third and fourth left interspaces Right heart catheterization at 11 months of age revealed a considerable rise in the pressure in the right ventricle, and almost the same pressure in the pulmonary artery When we re-examined him at 4 years of age I noted that the second sound over the pulmonary area was clearly diminished Since we couldn't explain these definite changes in the character of the second sound over the pulmonary area, the patient was recatheterized, and showed definite evidences of an infundibular stenosis (tables 1 and 2)

TABLE 1.—*Right Heart Catheterization*

| Blood Oxygen Contents, Vol. % | First Catheterization Age: 11 months B S A * = 0 36M² | Second Catheterization Age 4 years, 9 mos B S A = 0 62M² |
|---|---|---|
| Inferior Vena Cava | 8 97 | —— |
| Superior Vena Cava | 8 25 | 9 80 |
| Right Atrium | 8 32 | 9 64 |
| Right Ventricle | 11 3 | 12 1 |
| Pulmonary Artery | 12 3 | 13 1 |
| Left Ventricle | 13 3 | —— |
| Femoral Artery | —— | 14 9 |
| Oxygen Saturation | 95 6% | 91 2% |
| Hemoglobin Gm /100 cc | 10 6 | 12 1 |
| | PRESSURES mm Hg | |
| Right Atrium | (7) † | (6) |
| Right Ventricle | 66/6 | 89/2 |
| Infundibulum | —— | 17/0 |
| Pulmonary Artery | 56/18 (41) | 15/6 (11) |
| Pulmonary Wedge | (11) | —— |
| Left Atrium | (8) | —— |
| Left Ventricle | 69/3 | —— |
| Femoral Artery | —— | 83/49 (61) |

* B S A = Body Surface Area
† Numbers in parentheses = Mean Blood Pressure Levels

TABLE 2 —*Right Heart Catheterization*

| Calculated Blood Flows | First Catheterization Age 11 Months B S A = 0 36 M² | | Second Catheterization Age 4 Years, 9 Mos B S A = 0 62 M² | |
|---|---|---|---|---|
| | L/Min | L/M²/Min | L/Min | L/M²/Min |
| Systemic | 1 08 | 3 15 | 2 00 | 3 23 |
| Pulmonary | 4 39 | 12 2 | 4 04 | 6 59 |
| Shunt (left to-right) | 3 31 | 9 05 | 2 29 | 3 7 |
| Shunt (right to left) | —— | —— | 0 25 | 0 4 |
| Total Pulmonary Resistance (Dynes sec cm⁻⁵) | 747 | | 217 | |
| Total Pulm Resistance Index (Dynes sec cm⁻⁵) | 269 | | 133 | |

An angiocardiogram taken at 11 months of age revealed a definite blanching of the outflow tract of the right ventricle as a sign of left-to-right shunt at the ventricular level An angiocardiogram taken at 4 years of age showed a simultaneous visualization of the aorta and of a large pulmonary artery At this time, therefore, he had an additional shunt from the right ventricle into the aorta

My associates recatheterized about 30 patients and we found five additional patients whose findings are similar to the one cited here

We feel that some of these patients who have been described in the literature as cases of ventricular septal defect and pulmonary stenosis, an entity which is not too uncommon, and some patients who are the so-called acyanotic types of tetralogy of Fallot, may have originally manifested the clinical, angiocardiographic and cardiac catheterization findings of the patient presented here

We all know that many infants with large ventricular septal defects who are severely handicapped during the first year of life manifest striking clinical improvement after that age. The usual and most probable explanation for this improvement is that a satisfactory balance has been established between the systemic and pulmonary blood flows through the development of certain changes in the intima and media of the pulmonary arterioles The findings I have just presented in some of our patients lead us to believe that another mechanism may, at times, be responsible for this improvement. We feel that it is possible that a decrease in the left-to-right shunt at the ventricular level with a decrease in the pulmonary pressure may be due to the development of hypertrophy of the crista supraventricularis and of the parietal and septal bands of the outflow tract of the right ventricle.

KATZ I would like to ask Dr Shepherd, Dr Burchell or Dr. Edwards whether these new observations Dr Shepherd reported contradict the statements made by Dr. Edwards about the role of embryonic architecture in causing increased pulmonary resistance in some patients with shunts

EDWARDS Quite to the contrary, I think they fit in very well with the concept of septal defect which exists The relationship between the two ventricles and great arteries after birth is similar to that in the normal fetus before birth The regulatory mechanism for maintaining pulmonary flow is a function, at least after birth, of pulmonary vascular resistance

KATZ· Didn't Dr Shepherd imply there is an increase in resistance which develops de novo as a result of factors operating on the pulmonary vasculature?

EDWARDS I think that Dr Shepherd and I are in entire agreement with each other We both recognize that with free communication between the two circuits the systolic pressures remain about equal

The mechanism by which the resistance is maintained at a high level in the pulmonary circuit is not known to either of us The thick muscular arteries and arterioles are anatomic evidence of features which can be correlated with high resistance

These thick layers, I think, have two potential functions: (1) theoretically, they are capable of active constriction since they are composed of muscle and (2) the thick, small pulmonary vessels offer passive resistance It must take greater energy to force a certain amount of blood through a thick vessel than to force the same amount of blood through a thinner vessel

COURNAND· I would like to address a question to Dr Dawes, and to any of our expert pathologists who may be able to answer it. Do we know something about the bronchial circulation in the fetus? Have we any information based on injection, or any other technique, regarding its importance before and at birth?

LIEBOW: I am sorry that I have no contribution at the moment. Further studies are definitely indicated on this point Certainly in early embryonic life there is less disparity in the caliber of the pulmonary and bronchial vessels We know nothing about the flow In the pulmonary arteries it is much less than it is in adult life.

To change the subject, perhaps advisedly, I was interested in Dr. Gasul's comments in regard to possible hypertrophy of the wall of the right ventricle, and particularly the crista, to the extent of producing stenosis in the infant. On the left side, Sir Russell Brock (Functional obstruction of the left ventricle Guy's Hosp Rep, *106*,221-228, 1957) has recently observed that, in instances of severe stenosis of the aortic valve after apparently adequate surgical relief of that stenosis, there may still be such a large burgeoning into the lumen of the hypertrophied subvalvular portion of the left ventricle that the pressure drop is still very large from ventricle to aorta.

SARNOFF. I should like to ask Dr Dawes if he has any evidence to indicate that ganglionic blockade will interfere with constriction of the ductus on exposure to oxygen or whether the isolated ductus tissue, when suspended in bath, will contract or relax in response to changes of its oxygen?

DAWES: We have no observations with drugs which impede transmission through autonomic ganglia, but we have investigated the changes in diameter of the ductus in a preparation which consisted only of the heart and great vessels, including the ductus, and an artificial lung In this preparation, the ductus responded by constricting when the artificial lung was ventilated with oxygen, and dilated when it was ventilated with nitrogen It therefore seems likely that the effect of oxygen is directly upon the smooth muscle of the ductus

# Pulmonary Hypertension in Patent Ductus Arteriosus

*By* Rodolfo Limon Lason

The following observations are based on 128 catheterizations done in 148 cases of patent ductus arteriosus In explanation, I wish to state further that this work is being carried out by a very large team which draws from many hospitals in Mexico and quite a few in Central America This fact, and our active search, accounts for the disproportionately large number of cases of patent ductus with pulmonary hypertension which we are bringing before you today Our study shows that there is no sex difference in its incidence In 100 consecutive cases, classified by age groups, the patients with normal pressures and hypertensives are more or less equally distributed The largest groups are under 20 years of age The oldest patient in this study was a woman 62 years of age, who had a pulmonary pressure of 60/40 mm Hg The distribution of these 100 cases in relation to pulmonary pressure shows a range from one patient with a systolic pressure of 17 mm. Hg to one with a systolic pressure of 136, both of these are females Roughly one-third of the total number of selected cases have pressures over 80 mm Hg

I want to emphasize that patent ductus arteriosus with severe pulmonary hypertension is a progressive and fatal disease We have studied 6 cases during two or three successive catheterizations All are patients with pulmonary hypertension that refused operation the first time they came to the hospital, and when they later returned, their condition had become worse and did not permit surgical intervention

The first case we saw in February 1949 was a girl, 8 years of age She had a pulmonary artery pressure of 90/57 mm Hg, against an aortic pressure of 100/51 mm Hg Here the difference from right ventricle to pulmonary artery in oxygen content was 3½ volumes per cent She had very high pulmonary pressure, but she had a shunt from the aorta into the pulmonary artery and peripheral oxygen saturation in the right brachial artery was 76 per cent This is an unusual finding in uncomplicated patent ductus arteriosus and may indicate the presence of an additional defect or a reversal of the usual shunt In March 1953 her pulmonary artery pressure went up from 90/47 to 121/26 mm Hg and the aortic pressure was 120/63 The brachial artery and aorta had equal volumes per cent of oxygen There was no evidence of a shunt either way. We studied her again in June, 1957, and the oxygen content of the right brachial artery was 22 and of the femoral 19 volumes per cent. Oxygen saturation was 76 per cent in the brachial artery Now, if we perform a Valsalva maneuver on this patient, the difference in oxygen saturation between the right brachial and femoral artery will go up from 3 2 to 5 2 volumes per cent In other words, the maneuver will increase the right to left shunt In the light of our present experience we consider this patient to be inoperable.

Another case is that of a girl 23 years of age, first seen in 1949 with a pulmonary artery pressure of 113/54, and aortic 115/58. Aortic and pulmonary pressures were more or less alike, and she had a small arterial venous shunt. She refused operation, and in 1953 blood samples from the femoral artery and the right brachial artery were studied without catheterization. The oxygen contents of the right brachial and femoral artery were the same during normal respiration but when she performed the Valsalva maneuver there was a difference of 1.7 volumes per cent, the small amount being in the femoral artery.

She permitted herself to be catheterized again in March 1956. That was 7 years after the first study. The pressure had gone up from 115/54 to 130/60 mm Hg. Aortic pressure was more or less alike. She now has a venous arterial shunt. The difference between the right brachial artery and abdominal aorta is 2 volumes per cent. This patient also had evidence of a shunt on the other occasions when she was studied by direct puncture of the preductal segment, i.e., the right brachial artery, and the postductal segment, i.e., the femoral artery. Other cases showed great similarities.

Next, a girl 13 years of age had a typical patent ductus arteriosus. We saw her in 1944. In 1954, at the age of 23, we saw her again, and she had developed segmental cyanosis and swelling of the toes. During this interval the absolutely typical ductus had changed. The oxygen saturation was 29 volumes per cent in the right brachial artery. In the abdominal aorta the re-catheterization oxygen went down from 29 to 24.3 volumes per cent, and saturation was only 80 per cent, the pressures were 126/96 mm Hg with a mean of 108 in the pulmonary artery, whereas in the earlier study it was only 104/86 with a mean of 94 mm Hg.

These cases of ductus arteriosus with severe hypertension have two fundamental types of cyanosis. They may have a segmental type of cyanosis which is due to the functioning of a shunt from the pulmonary artery to the lower segment of the body through the ductus, and others present a generalized cyanosis. This generalized cyanosis and blood unsaturation is not modified by surgery.

We have 5 patients who have had generalized cyanosis. Of these 5 patients, only 2 have been operated on. One of them was seen on three successive occasions. The last time we saw him, last month, we did a third catheterization on him, however, we had to draw the catheter out and we did not take any blood samples. He has generalized cyanosis now, and a pulmonary pressure much above the aortic.

The other patient who has been operated on was a woman, she improved greatly. On 13 studies we have done of this patient's arterial saturation over a period of 7 years, she has always had a saturation which oscillates between 68 and 74 per cent. The three postoperative studies have shown that she still retains this unsaturation. We don't know whether she has any other added congenital defect because her pressure has increased; she has no murmur and she feels much better.

The gradient of pressure alone is not the only factor concerned with the inversion of a shunt, as is demonstrated in another patient with 11 mm Hg pressure difference where there was no blood shunted even during the Valsalva maneuver.

Now we shall proceed to the discussion of the operated cases. There were 27 cases with severe pulmonary hypertension whose pressures ranged from

above 90 mm. Hg or with gradients no greater than 11 mm. when aortic pressure was lower than 99. We consider the patient to have pulmonary hypertension even if the pulmonary pressure is only 70 mm Hg, when the aortic pressure is as low as 65

Another group of 14 patients with pulmonary pressures equal to or above aortic were operated on They had no shunts, or small shunts in either direction. These 14 cases all were very severe, but only one died

We have had 21 patients with pure venous arterial shunts, with no evidence of left to right shunts Only three of this group have been operated upon The operations were performed under duress, for the patients actually demanded the operation The results have been disastrous three operated on—three dead. Unless some method is found in which pulmonary pressure may be brought down, I would warn against operating on such patients

We have followed 25 patients with pulmonary hypertension who have been operated upon for patent ductus

A boy 16 years of age, Grade D, was one of several patients with systemic arterial hypertension The next patient was a hypertensive, 65 years of age Five years and 4 months after his operation he had a fairly large residual hypertension Another patient, a child 10 years of age and 29 months postoperative, still has residual hypertension These patients with hypertensive vascular disease in addition to their patent ductus do not respond well to operations One of two exceptions was a child 4 years of age in whom systemic arterial pressure returned to normal postoperatively

One patient has developed primary pulmonary hypertension or ordinary pulmonary hypertension, but she had an arteriovenous shunt before the ductus was closed When the ductus was closed the patient, age 11, was extremely small Her whole condition improved immensely until one year later At that time a complete change occurred and she has since developed cyanosis and is going downhill steadily

The other 21 cases follow more or less the same pattern, and they all have some residual hypertension We have 4 more cases which are very similar, except for one patient, a boy, who has equal aortic and pulmonary pressures This boy was studied seven months after operation, and his pressure was down to normal

We have always held that pulmonary hypertension in the case of ductus arteriosus is not conditioned exclusively by an extra amount of blood going through the lungs They must have some abnormal factor in their lungs which, on being excited by this stimulus, results in increased pressure There are some ducti which have very high pressures in spite of the fact that they have small lumina

I would like to end with one final note, that the duration of extra flow in normal lung tissue is irrelevant, we believe, to the development of pulmonary hypertension One patient who was 45 years of age had pulmonary hypertension but not as high as those of some children we have described Moreover, this patient came back when she was 57 years of age with something remark-

able to say: "Doctor, I feel very much better now" When we catheterized her the pulmonary artery pressure was down to 15 mm Hg

In conclusion it can be said that patients with severe pulmonary hypertension and right to left shunts in the presence of patent ductus arteriosus are poor surgical risks and probably should not be operated on until some means is found to lower pulmonary tension and reverse the flow in the shunt.

above 90 mm. Hg or with gradients no greater than 11 mm. when aortic pressure was lower than 99. We consider the patient to have pulmonary hypertension even if the pulmonary pressure is only 70 mm. Hg, when the aortic pressure is as low as 65.

Another group of 14 patients with pulmonary pressures equal to or above aortic were operated on They had no shunts, or small shunts in either direction These 14 cases all were very severe, but only one died

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wall tension They are readily distensible, the degree of distensibility being limited by the jacket of fibrous tissue which composes adventitia As a part of the aging process, medial elastic fibers and muscle cells are gradually replaced by fibrous tissue Consequently, active tension in the vessel wall decreases and there is an increased dependence on the nonelastic fibrous tissue to limit vessel distensibility.

Extravascular pressure, that is, pressure exerted on the outer wall of the vessel by body substance which tends to reduce vessel diameter is kept to a minimum by the presence of air, not fluid, in the alveoli and the rhythmic shifts from positive to negative intrathoracic pressure Distal to the small pulmonary arteries lies a vast network of capillaries literally suspended in air and supported only by their endothelial lining and the alveolar wall These vessels readily adapt themselves to alterations in flow. Open pulmonary capillaries visualized under the microscope constantly vary in number under normal circumstances and the total shift in the number open may be accentuated by hypoxia, carbon dioxide and various vasopressor agents

The relationship of pressure and flow in this readily distensible system is to all intents and purposes nonexistent under normal conditions Flow may be increased threefold without a significant rise in pressure However, when the point of maximal distensibility of the vascular bed is reached, a linear relationship appears No longer distensible, the system acts more like a series of rigid tubes Each increment of flow adds an increment of pressure. Thus, as flow is increased, a relatively flat pressure curve is maintained until a critical flow level is reached and then pressure and flow increase proportionately It should be emphasized here that blood flow to an area of lung may be increased either by increasing cardiac output or by decreasing the functioning vascular bed

The newborn lung, in contrast to the normal adult lung, is characterized by a close relationship of pressure to flow The small pulmonary arteries and arterioles are muscular vessels with an abundance of medial muscle cells and a relative and absolute increase in elastic fibers Vessel lumens are small The potential force present in the walls of the infant vessels is greater than that of the adult. The small diameter permits the vessels to withstand much higher intraluminal pressures without marked dilatation or injury The explanation of this difference is clear The fetal lung is an integral part of the systemic circulation whereas, after birth, the pulmonary circulation becomes a separate system. The newborn lung represents a transitional stage, a stage of gradual disuse atrophy of the muscle of the pulmonary vessels Because of size and wall thickness, an increase in flow leads primarily to an increase in pressure rather than an increase in vessel diameter The work of Dawes and his associates demonstrates the close relationship between flow and pressure in the newborn lamb lung A small increase in aortic-pulmonary flow through a constricted ductus caused a clear increase in pulmonary artery pressure

There are additional factors which help to establish this close relationship between flow and pressure in the newborn lung Total lung size is probably relatively less in the newborn so that less flow is necessary to reach the limit of distensibility Furthermore, at least in the early hours of life, alveoli are not

# The Relationship of Flow to Pressure in Various Types of Congenital Heart Disease, Particularly Those Associated with Pulmonary Hypertension

*By* J. Francis Dammann, Jr.

An understanding of the relationship of pulmonary blood flow to pulmonary blood pressure in congenital heart disease is made difficult by the lack of a suitable experimental preparation that includes a cardiac defect *which can increase pressure without altering flow* (except by obstructing pulmonary venous return) or increase flow significantly without altering pressure. Thus, *our reasoning must be based on clinical information supplemented* by meager experimental data. As a result, divergent and apparently irreconcilable hypotheses have been advanced.

Pulmonary vascular damage in patients with a ventricular septal defect has been said to represent either an associated congenital defect, to be the result of high flow, or to be the result of pressure transmitted from the systemic circulation through the defect to the lungs. If one subscribes to any of these views, how can the high flow auricular defect with normal pulmonary artery pressure or the low flow defect with pulmonary hypertension be explained? *Is there a further explanation for these various clinical patterns? The explanation* is to be found, I believe, in an appreciation of the fact that flow, pressure, and vascular injury do not always relate in a similar manner.

The relationship of blood flow and pressure cannot be discussed except within the framework of the anatomic and functional characteristics of the pulmonary vascular bed. The factors which influence this relationship are not only the size and position of the cardiac defect, the total area of the pulmonary vascular bed, the lumen size, and the wall thickness of the pulmonary vessels. The stage of development of the normal adult pulmonary vasculature at which *significant alterations in either pressure or flow occur must also be included.* Thus, a defect which exerts significant stress at birth may establish a different relationship between flow and pressure than one that becomes significant after the adult pulmonary vascular bed has been developed. The normal lung contains a low pressure, highly distensible vascular bed, one which can accommodate a threefold increase in flow with little or no change in mean pulmonary artery pressure. Pulmonary resistance decreases if pulmonary blood flow is increased acutely. This means *that there is either an increase in diameter of* the existing patent vessels or an increase in the number of functioning vascular channels. The smaller pulmonary arteries and arterioles, in contrast to the thick-walled and relatively small-lumened arterioles of the systemic circulation, are thin-walled and large-lumened and capable of only minimal active

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and the opening up of the alveolar capillary bed The volume of shunt is sufficient to utilize the expanded vascular bed and therefore pulmonary arterial pressure does not fall to normal Provided the shunt is limited by the size of the defect, pressure may gradually fall towards normal as heart and lung size increase and the vascular bed becomes sufficiently large to encompass the increased pulmonary blood flow The retention of an elevated pulmonary artery pressure after birth does not permit normal disuse atrophy of the muscle of the pulmonary vessels They remain relatively thick-walled and small-lumened Thus, the linear relationship of pressure and flow is maintained or else becomes manifest at a lower flow rate than in the normal adult lung This difference in the stage of pulmonary vascular evolution at which the lung is subjected to stress explains why there is usually a normal pulmonary artery pressure and a very high flow in the simple auricular defect, and yet a somewhat elevated pressure at a much lower flow level in the moderate sized ventricular defect

The tiny ventricular defect and the usual small patent ductus do not permit a sufficiently high flow to retain an elevated pulmonary artery pressure except, perhaps, for the first few days of life Thus, in terms of the pulmonary vasculature, they resemble the auricular defect On the other hand, because the shunt is large shortly after birth, the septum primum defect with mitral insufficiency or the total anomaly of the pulmonary venous return resembles the moderate sized ventricular defect

When the ventricular defect or communication between the great vessels is sufficiently large so that it, itself, does not limit the volume of shunt, a common systolic pressure or common ejectile force exists in both the aorta and pulmonary artery Flow to the two circulations, then, is totally dependent upon peripheral resistance, a situation comparable to that present in the fetus In terms of flow, peripheral resistance is expressed in the diastolic pressure level Since mean pressure integrates both systolic and diastolic, a drop in pulmonary vascular resistance must not only lead to an increase in pulmonary blood flow but a decrease in mean pulmonary artery pressure By the same token, a decrease in systemic resistance causes an increased systemic blood flow, a decreased pulmonary flow, and a decrease in both systemic and pulmonary artery mean pressure It becomes apparent that the relationship of pulmonary artery flow and pressure in the presence of a large communication between the two circulations cannot be discussed as an isolated relationship but must be discussed in terms of the total circulation The position of the lungs in the total circulation becomes comparable to any other organ such as the brain, kidney and heart, instead of being separate and distinct Yet the vascular bed of the lungs is much less protected than that of other organs Following birth, since fluid has been replaced by air in the alveolar sacs, much of the supporting structure of the smaller pulmonary vessels has been removed This occurs at a time when pressure in the total circulation is raised because the low resistance placental vascular bed is shut off. It is small wonder that the stress on the lungs is frequently excessive The effect of strain is either progressive vascular dilatation, an acute injury response, or an acute arteritis The result of dilatation is a progressive de-

totally emptied of amniotic fluid and distended with air. Thus, extravascular pressure is increased, and acts as an additional force directed against vessel enlargement Finally, there is, I believe, good evidence that the increased thickness of the media permits a more efficient response to vasomotor stimulus The thickness of vessel wall adds a protective factor to the vascular bed. When pressure rises and the vessel is acutely stretched, rupture of the wall is less likely to occur. Instead, further hypertrophy of vessel wall develops usually not associated with significant intimal damage.

Pulmonary vascular disease of significant proportions still further alters the interrelationship of flow and pressure The vascular changes both reduce vessel distensibility and reduce the total number of patent vascular channels Consequently, the pulmonary vascular bed functions like a system of rigid tubes A small increase in flow is accompanied by an increase in mean arterial pressure.

Thus, in the normal adult lung, pulmonary blood flow and pressure bear little relationship to each other until high flows occur and the vascular bed has been totally utilized A linear relationship is demonstrable at a much lower flow in the newborn lung and, in the presence of severe pulmonary vascular disease, any increase in flow leads to an increase in pressure How does this concept aid in understanding congenital malformations of the heart in which there is a potential shunt without pulmonary stenosis? In the early months of life, the left-to-right shunt through a simple auricular defect is small as indicated by the relatively normal heart size, slightly increased right ventricular chamber size and normal electrocardiogram Since the shunt is minimal in infancy, the pulmonary vascular bed undergoes disuse atrophy and evolves in a normal fashion As the shunt gradually increases with the passage of time, the additional flow is accommodated by passive dilatation of already patent vessels and opening of new channels without a rise in pressure Blood pressure does not rise until the shunt has reached tremendous proportions or until the total pulmonary vascular bed has been significantly reduced by repeated parenchymal infections In our experience with a series of patients with an auricular defect, pulmonary hypertension and pulmonary vascular disease, vital capacity and maximum breathing capacity were reduced an average of 50 per cent and all patients gave a history of repeated pulmonary infections Once pressure has become elevated, a vicious cycle is precipitated The thin-walled nature of the poorly supported pulmonary vessels makes them particularly susceptible to injury Intimal thickening associated with some degree of medial hypertrophy reduces the caliber of the vessels increasing pulmonary resistance and necessitating a still greater propelling pressure The relationship of flow and pressure changes rapidly to that associated with pulmonary vascular disease When the right ventricle fails, filling pressure rises, and the shunt is reduced and eventually may reverse This sequence of events may be surprisingly rapid, and an argument in favor of early surgical closure

In contrast, through a moderate sized ventricular defect or patent ductus, a significant shunt occurs as soon as pulmonary vascular resistance drops following lung expansion, the replacement of alveolar amniotic fluid with air,

Evidence of arterial injury was found in about one third of the patients who died shortly after a systemic-pulmonary anastomosis was created. The lesions can be divided into three stages of increasing severity.

1. Distention of the small pulmonary arteries and arterioles, with stretching of the vessel wall (fig. 1)

2. Escape of red blood cells from the lumen, presumably through minute areas of rupture of the vessel wall (fig. 2)

3. Frank rupture of small pulmonary arteries (fig. 3). The extravasated blood disrupts the layers of the arterial wall and separates the adventitia from the media.

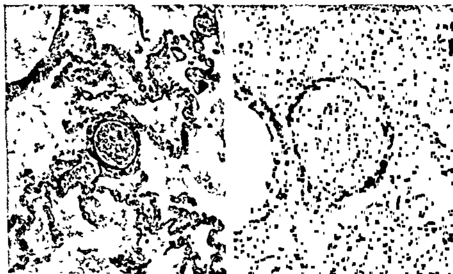


FIG 1.—(*left*) Small pulmonary artery from a 5 year old boy with tetralogy of Fallot who died of cerebral anoxia after a subclavian-pulmonary arterial anastomosis. Note the distention of the vessel, stretching of the arterial wall, and capillary congestion
Elastic tissue stain x300

FIG. 2.—(*right*) Small pulmonary artery from a 2 year old girl with tetralogy of Fallot who died of cerebral thrombosis 36 hours after an innominate pulmonary arterial anastomosis. Note red blood cells in between fibers of adventitia and marked capillary congestion
Elastic tissue stain x300

In most instances the capillaries are markedly congested and may rupture also. These lesions may be associated with evidence of venous congestion and pulmonary edema, but in many instances they were found in the absence of cardiac failure, in patients who died of other causes (cerebral anoxia, aspiration and hemorrhage) in the immediate postoperative period.

The important question concerns the fate of these lesions if the patient survives. Do they initiate changes in the vessel wall, which may gradually result in narrowing of the pulmonary arterial bed? To date we have not been able to trace the sequence of events which follow arterial injury in the lungs.

Among the patients who died 1 to 11 years after operation late fibrotic

crease in pulmonary vascular resistance despite the maintenance of a relatively constant systolic pressure, an increase in the percentage of total cardiac output directed to the lungs and frequently, death in high output failure or acute pulmonary edema The result of arteritis is progressive luminal narrowing due to medial hypertrophy and intimal thickening, a decrease in pulmonary blood flow despite the maintenance of a relatively fixed systolic pressure. The relationship between pressure and flow in the presence of a large ventricular defect would appear, therefore, to be opposite to those previously discussed. A rise in mean pulmonary artery pressure is accompanied by a decrease in flow instead of resulting from an increase in flow.

In this discussion, I have dealt with a few of the complexities involved in an understanding of pulmonary pressure-flow relationships. It is, I believe, apparent that the relationship is neither the same for all malformations nor is it constant in each malformation We are dealing with a dynamic and ever-changing system, particularly so when the pulmonary circulation is directly a part of a changing systemic circulation Our understanding cannot be complete unless it includes the part played by all factors The important factors I have discussed are (1) size, characteristics and evolution of the vascular bed, (2) size and position of the cardiac malformation, and (3) the importance of the systemic circulation In the future, the role played by changing vasomotor tone must be evaluated and fitted into the total picture. Perhaps then we will be in a better position to predict the patient's clinical course and select the ideal time for correction of the underlying defect

## Discussion

Ferencz I would like to show briefly some pulmonary vascular changes which may occur in another kind of patent ductus one created artificially for the relief of symptoms in patients with tetralogy of Fallot and similar malformations

First it must be mentioned, that in these malformations alterations in the pulmonary vascular bed may be found in patients who have not been operated upon Dr Rich has described these thrombotic lesions, which are present in various stages of organization, and which can result in significant, often severe, narrowing of the pulmonary vessels. In our recent studies we have attempted to relate the presence of these lesions to the age of the patient and the degree of polycythemia, but have found no clear cut correlation We did find, however, that in patients with moderately severe thrombotic changes, a history of spells of paroxysmal dyspnea was twice as frequent as in those who had only mild lesions or none at all This would suggest that the episodes of paroxysmal dyspnea, in which the pulmonary blood flow is slow, contribute significantly to the occurrence of intravascular thrombosis

Pulmonary vascular changes observed following shunting operations are entirely different in nature They are similar to those shown to us yesterday by Dr. Ferguson and Dr Dammann in connection with their experimental work, and similar, also, to lesions of the mesenteric arteries noted in some patients following resection of a coarctation of the aorta

# Pulmonary Hypertension Developing in Atrial Septal Defect

*By* Lewis Dexter

Atrial septal defect is characterized by a defect in the septum between both atria which, if sufficiently large, results in a free communication between these two chambers Although there is presumably little shunting at birth, a left-to-right shunt does develop early in life from left atrium to right atrium. Eventually the shunt, and therefore pulmonary blood flow, may be enormous This shunt passes via the right ventricle, through the lungs, back to the left atrium, resulting in a torrential pulmonary blood flow[1] Calculation of these huge pulmonary blood flows by the Fick principle is fraught with error because of the narrow pulmonary arteriovenous oxygen difference Whether they are 20, 25 or 30 liters per minute makes little difference

The findings in a case of uncomplicated atrial septal defect are illustrated below Note that the calculated pulmonary blood flow was 11 6 liters per minute, the pulmonary arterial pressure was slightly elevated, and the pulmonary vascular resistance was calculated to be well within normal limits

Table 1 —*Findings in Case I of Atrial Septal Defect*

| V C age 19 | Oxygen cc /L | Pressure, mm Hg |
|---|---|---|
| Femoral artery | 194 (98%) | 122/82 (95) |
| Left auricle | 194 | 6 |
| Pulmonary vein | 192 | 7 |
| Pulmonary "capillary" | 193 | 7 |
| Pulmonary artery | 177 | 38/12 (23) |
| Right ventricle | 182 | 38/6 |
| Superior vena cava | 140 | |
| Body surface area | 1 56 sq M | |
| Oxygen consumption | 198 cc /min | |
| Peripheral blood flow | 3 7 L/min | |
| Pulmonary blood flow | 11 6 L /min | |
| Shunt, left-to right | 7 9 L /min | |
| Pulmonary vascular resistance | 68 dynes sec cm $^{-5}$ | |

The findings in a second individual are shown on p 228 Note that there was arterial oxygen unsaturation, some shunting from left-to-right and from right-to-left, the pulmonary blood flow was low, the pulmonary arterial pressure very much elevated, and the calculated pulmonary vascular resistance of 1230 dynes seconds cm$^{-5}$ was between 15 and 20 times the normal At postmortem examination, this patient had a large ostium secundum type defect All the vascular changes in the large arteries, small arteries and arterioles that were

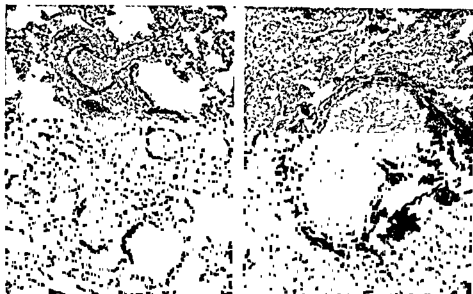


FIG 3 —(*left*) Small pulmonary arteries of a 21 month old boy with tricuspid atresia who died suddenly following a convulsion 24 hours after a subclavian pulmonary arterial anastomosis. Note rupture of arteries with massive extravasation of blood disrupting the adventitia *Elastic tissue stain. x150*

FIG 4 —(*right*) Small pulmonary artery from a 16 year old boy with tetralogy of Fallot who died 9 years after a subclavian pulmonary arterial anastomosis, which was patent at autopsy Note marked fibrosis of arterial wall and narrowed lumen
Elastic tissue stain x150.

changes were observed in about one third I would like to show just one example of these Figure 4 shows a small pulmonary artery of a 16 year old boy, who died 9 years after a subclavian-pulmonary anastomosis was performed He had a good result from the operation, with a good continuous murmur for 6 years and then a gradual diminution of the murmur of the anastomosis and return of cyanosis At autopsy the anastomosis was patent, but the pulmonary arteries showed extensive fibrosis and obstruction of the lumens

*We do not know what relation, if any, there is between the injury changes* noted early and the occurrence of arterial narrowing many years after operation.

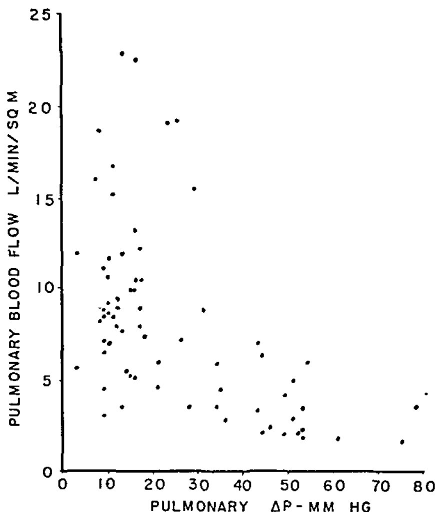



FIG 1.—The relationship of pulmonary blood flow to the pressure difference across the lung (pulmonary arterial mean pressure minus the left atrial, right atrial, *or* pulmonary "capillary" wedge pressure) Note that at high flows, there is an inconstant tendency to increased pressure At high pressures, the flow is invariably reduced

20 up into the sixth decade of life have any definite elevation of pulmonary vascular resistance The lines joining two dots in figure 2 illustrate the progressive nature of this disorder once it has appeared, these being the only cases of the group that have been restudied at a later date The highest resistance encountered was some 35 times the normal, a fantastic increase of pulmonary vascular resistance

I shall not attempt to discuss the circulatory consequences of the increased resistance in this disorder, but would rather emphasize this peculiar behavior of the late development of pulmonary vascular resistance in atrial septal defect. The question arises as to why there should be such a delay in its occurrence As we have heard,[2,3,4] the increased pulmonary vascular resistance of a

discussed yesterday were present, and in addition there was a large thrombus occluding the left main pulmonary artery and all its major ramifications There were scattered thrombi throughout the vasculature of the right lung There appeared to be only a few major channels left to accommodate the pulmonary blood flow.

TABLE 2.—*Findings in Case II of Atrial Septal Defect*

| K R age 45 | Oxygen cc./L. | Pressure, mm.Hg |
|---|---|---|
| Femoral artery | 165 (86%) | 120/75 (90) |
| Left auricle | | 5 |
| Pulmonary vein | 188 (98%) | |
| Pulmonary artery | 131 | 83/3 (31) |
| Right ventricle | 133 | 83/5 |
| Right auricle | 133 | 5 |
| Superior vena cava | 115 | |
| Body surface area | 1.54 sq M | |
| Oxygen consumption | 171 cc /min | |
| Peripheral blood flow | 3.4 L /min. | |
| Pulmonary blood flow | 3 0 L /min | |
| Shunt, left to right | 0 7 L./min. | |
| Shunt, right to left | 1.1 L./min | |
| Pulmonary vascular resistance | 1230 dynes sec. $cm.^{-5}$ | |

Thus, pulmonary vascular disease, i e, obstruction to blood flow through the lungs, is a major complication of atrial septal defect The relationship of pulmonary blood flow to the pulmonary arterial-left atrial pressure difference is illustrated in figure 1 It will be seen that at high flows there is a tendency for the pulmonary arterial pressure to be elevated, but only to a modest extent and even then not uniformly so Three of the patients with the highest calculated pulmonary arterial flows had normal pressures, whereas another 3 had definitely elevated pulmonary arterial pressures but these did not exceed 30 mm Hg As the pulmonary arterial-left atrial pressure difference became higher, pulmonary blood flow was lower, and at the highest pressures the pulmonary blood flow was either normal or below normal It is concluded, therefore, that at very high pulmonary blood flows there may be a modest increase of pulmonary arterial pressure, although this has not been a uniform finding, and that there is an inverse relationship between the height of the pressure difference across the lung and the pulmonary blood flow

Figure 2 illustrates the relationship between calculated pulmonary vascular resistance and the age of the patient It will be seen that in no instance has a definite elevation of pulmonary vascular resistance been observed before the age of 20 This has been well borne out by the published literature, and I know of only 2 or 3 instances of a definite increase of pulmonary vascular resistance in childhood among patients with a secundum type of defect It is concluded, therefore, that under the age of 20 pulmonary vascular disease is an exceedingly rare complication of atrial septal defect of the secundum type and, from figure 2 it can be seen that only about half of the cases over the age of

As shown in figure 1, the higher the pressure in the pulmonary circuit, the lower the pulmonary blood flow. In several of our cases with severe pulmonary vascular disease, extensive thrombosis of the pulmonary vasculature has been prominent, and this has been a frequent finding in the literature.[5,8] I know of no evidence to indicate whether this is an early or a late process, i.e., whether this initiated the pulmonary vascular obstruction or whether it is a late phenomenon aggravating the pulmonary vascular obstruction. It is certainly possible that as the pulmonary blood flow decreases, there may be a tendency to the production of stagnant thrombosis, such as occurs in the left atrium in mitral stenosis.

Finally, there is a possibility of diffuse vasoconstriction in these cases, concerning which I have no information but I believe Dr. Burchell[9] will discuss this in the ensuing paper.

One factor other than pulmonary hypertension appears to be responsible for a reduction of right ventricular output. A number of patients have been observed without pulmonary hypertension whose right ventricular output has increased considerably after the administration of digitalis, indicating that the right ventricle had been malfunctioning and unable to eject its full contents during systole, i.e., it had failed, and that following the administration of digitalis the stroke output increased notably. It is postulated that the reduced right ventricular output, whether on the basis of pulmonary hypertension or on the basis of failure from the long-continued work load from its high output, predisposes to stagnant thrombosis in the lungs.

In summary, it would appear that the late development of pulmonary vascular disease in patients with atrial septal defect may be due to a variety of factors. Although the initiating factor is not entirely apparent, there would

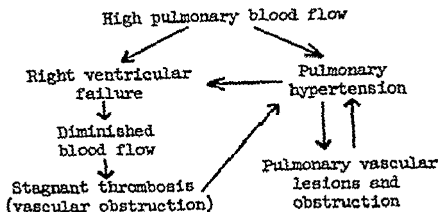



FIG 3.—Hypothesis of genesis of pulmonary vascular disease in atrial septal defect. Schema to demonstrate some of the factors which produce progressive vascular disease in atrial septal defect. See text for discussion.

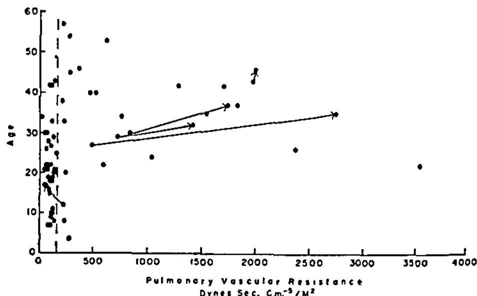



FIG. 2 —The relationship of pulmonary vascular resistance to age Note that under the age of 20, no definite increase of resistance is seen Over the age of 20, about half of the cases have an increased resistance and the other half do not The dots joined by arrows show the rising resistance with time, indicating the progressive character of pulmonary vascular disease in patients with atrial septal defect

ventricular septal defect is prompt to appear in infancy and childhood In this condition, there is a high flow as well as a high pressure in the pulmonary circuit from birth In atrial septal defect there is a very high flow occurring not at birth but some time after birth, accompanied by an essentially normal pressure Perhaps it is just this—the high flow and normal or only mild elevation of pulmonary arterial pressure—that takes twenty years or more to produce pulmonary vascular disease

*Patients with atrial septal defect are notorious for their susceptibility* to respiratory infections Dr Dammann [4] has mentioned that some of these individuals develop pulmonary ventilatory disturbances, which might be an added factor in the genesis of their pulmonary vascular disease Unfortunately, I have made no observations on this point in my own patients

It has been suggested that pulmonary embolism may play a rôle here Pulmonary embolism is rare in the first two decades of life and begins to become apparent in the third decade However, I have been unable to detect any evidence that pulmonary embolism has occurred in any of our patients with pulmonary vascular disease, and if this is a factor, I suspect it is rare

Some sort of vascular change begins to become apparent in about the third decade of life. Coronary disease, thrombophlebitis and pulmonary embolism, ... systemic circuit. In the lesser ...nerally appear in the trilogy ...ntricular septal defect, but whether or not the delayed appearance of pulmonary vascular disease in atrial septal defect is temporally related to some concomitant disturbance in the pulmonary vasculature, I do not know.

# The Application of Arteriography to the Pathological Study of Pulmonary Hypertension

*By* D. S. SHORT

ALTHOUGH OUR KNOWLEDGE of the pathology of the pulmonary arteries in pulmonary hypertension has advanced greatly in the past decade, the contributions hitherto have been qualitative rather than quantitative We still have not answered the important question How extensive is the arterial disease, and to what extent does it account for the resistance to blood flow through the lung in pulmonary hypertension?

It is widely believed that the arterial disease demonstrated at necropsy is insufficient to account for the high vascular resistance present during life Random histological sections do not, however, reveal the true extent of arterial disease for they do not provide an adequate picture of the arterial bed as a whole Pulmonary arteries are sometimes occluded for short distances only, and appear normal in sections taken above and below the point of obstruction (Spencer, *1950*) Moreover, branches otherwise healthy are frequently constricted at their origin by intimal proliferation in the parent artery (Harvey, *1956*) Such focal narrowing may be missed unless literally hundreds of sections are examined (fig 1)

Arteriography offers a means of displaying the arterial bed of the lung in its entirety

In *1951*, William Evans of the London Hospital established the value of pulmonary arteriography as an adjunct to histology and showed a generalized depletion of the finer pulmonary arteries in various kinds of pulmonary hypertension

Since *1952*, Evans and I have together studied the pathology of pulmonary hypertension by a combination of arteriography and histology in mitral stenosis (Evans and Short, *1957*), congenital heart disease (Evans and Short, *1958*) and (in association with Evan Bedford) in primary (or solitary) pulmonary hypertension (Evans et al , *1957*)

This communication is based on the results of 70 pulmonary arteriograms performed either at the London or the Middlesex Hospital Thirty-five of the cases had established pulmonary hypertension, and 35 were controls The diagnosis of pulmonary hypertension was made on clinical grounds, and confirmed by the finding at necropsy of a right ventricular wall at least 7 mm thick, the normal being 3 to 4 mm Approximately half the patients were investigated during life by cardiac catheterization which also confirmed the presence of pulmonary hypertension Most of the patients with pulmonary hypertension had been disabled for at least a year, but a few died within six months of the onset of symptoms

appear to be at least two vicious circles established for its continuation, as indicated in figure 3 The high pulmonary blood flow may lead to a mild degree of pulmonary hypertension, which eventually results in the appearance of vascular lesions, which in turn promote further pulmonary hypertension, this circle being a continuous one. High pulmonary blood flow or pulmonary hypertension may at the same time produce right ventricular failure with diminished blood flow, stagnant thrombosis, and then the production of further pulmonary hypertension In any event, once this process of pulmonary hypertension starts, it appears to be a progressive one, interfering with the success of surgery and leading eventually to the death of the patient.

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TABLE 1.—*Cases Investigated by Post Mortem Arteriography*

| Diagnosis | Number | Pulmonary Hypertension |
|---|---|---|
| Mitral stenosis | 18 | 9 |
| Congenital heart disease | 9 | 5 |
| Other varieties of heart disease | 8 | 3 |
| Chronic lung disease | 13 | 8 |
| Solitary pulmonary hypertension | 7 | 7 |
| Recurrent pulmonary embolism | 2 | 2 |
| Systemic hypertension | 4 | 1 |
| Miscellaneous | 9 | 0 |
| Totals | 70 | 35 |

the arteriogram should reflect only structural changes in the arterial bed This was therefore carefully checked by histological examination In the uninjected lung, the elastic laminae were always more or less deeply crenated, but after a satisfactory injection, the arterial wall was much thinner in relation to the size of the lumen and the elastic laminae were quite smooth In practice, full distension was achieved by heating the suspension to 80° C , and injecting it at a pressure of 50 mm Hg In cases of pulmonary hypertension, a pressure of 100 mm Hg was used

To display the smallest arterioles adequately arteriograms must be magnified by at least 15 diameters Barclay (*1947*) showed that by using Kodaline Standard Film the desired magnification could be obtained with only slight modification of the usual radiographic technique

## FINDINGS

Pulmonary arteriography proved helpful in differentiating pulmonary arteries from bronchial arteries and pulmonary arterioles from venules at subsequent histological examination In spite of Verloop's (*1948*) clear description of the normal bronchial arteries, these vessels have often been mistaken for obstructed pulmonary arteries In mitral stenosis, the venules are narrowed by a subendothelial deposition of eosinophilic material and they have frequently been mistaken for narrowed arterioles

Pulmonary arteriography was also valuable in demonstrating abnormal anastomoses, both between pulmonary and bronchial arteries, and also between branches of the pulmonary arteries

The most important information provided by the arteriogram concerned the extent to which the pulmonary arterial bed was reduced by organic disease In the absence of pulmonary hypertension, there was never any significant reduction in the pulmonary arterial bed although often a few small arteries were occluded, and sometimes a segmental artery was obstructed In established pulmonary hypertension, on the other hand, the pulmonary arterial bed was always greatly reduced even when symptoms had been present for only a few months

In cases of *recurrent pulmonary embolism*, the pulmonary arteriogram showed large filling defects due to occlusion of segmental arteries In places of

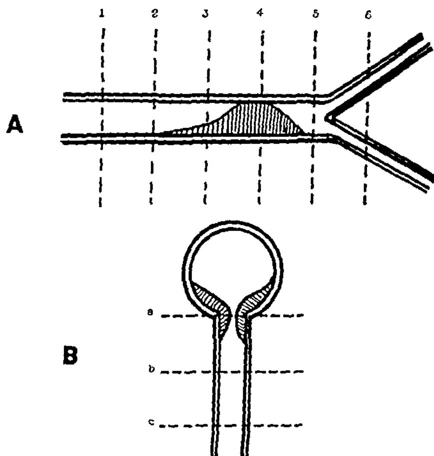



*Fig 1.—The inadequacy of routine histological sections in the demonstration of focal arterial block*

A. Occlusion proximal to arterial bifurcation
*Section taken at 4 would show occlusion, and at 3, narrowing, but sections taken at 1, 2, 5, and 6 would show a normal lumen*

B. Stenosis at the origin of a side branch
*Section taken at a would show narrowing, but sections taken at b and c would show a normal lumen.*

*In both cases, arteriography would demonstrate the obstruction because the injection medium would be unable to pass it.*

## Method

At necropsy, one lung was removed intact and kept for arteriography The other was examined in the usual way, from three to ten blocks being retained for microscopy. Sections were routinely stained with Verhoeff's elastic stain as well as with haematoxylin and eosin The technique of arteriography has been described in detail elsewhere (Short, *1956*), so only a brief outline will be given here

The radio-opaque medium used (a bismuth oxychloride-gelatin suspension) was one which penetrates to vessels of 30 microns, stopping just short of the capillaries It therefore fills most of the resistance vessels of the lung

The suspension was heated, and injected at such a pressure that the arteries

| CLASSIFICATION | ELASTIC ARTERIES OVER 1.0 mm DIAM | MUSCULAR ARTERIES 0.1 - 1.0 mm DIAM | ARTERIOLES UNDER 0.1 mm DIAM |
|---|---|---|---|
| RECURRENT PULMONARY EMBOLISM | | | |
| CONGENITAL HEART DISEASE | | | |
| SOLITARY PULMONARY HYPERTENSION | | | |
| MITRAL STENOSIS | | | |

*Fig 2.—The size of artery obstructed in different varieties of pulmonary hypertension*

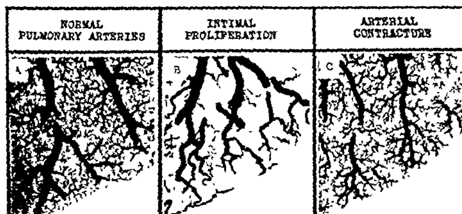



*Fig 3.—The two forms of organic peripheral arterial narrowing in pulmonary hypertension*

A Contact print from section of normal lung 1 cm thick after injection of bismuth oxychloride gelatin suspension into main pulmonary artery of intact lung (approx life size)

B Arteriogram, prepared in same way as A, in pulmonary hypertension, showing many arteries blocked by intimal proliferation (approx life size)

C Arteriogram, prepared in same way as A, in pulmonary hypertension, showing arteries diffusely narrowed by contracture (approx life size)

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## Discussion

### *The Effect of the Observed Arterial Narrowing on Resistance to Blood Flow through the Lung*

Both types of arterial narrowing might be expected to cause a serious increase in resistance to blood flow through the lung. When most of the peripheral arteries are occluded and the circulation through the lung is virtually maintained by abnormal collateral channels, the functional effect is obvious. When there is merely a generalized diffuse narrowing of the arteries, the appearances are not so striking, but the effect is probably just as great

actual infarction, the injected material collected to form dense irregular blotches resembling birds' nests.

In *mitral stenosis*, the arteriogram was abnormal whether pulmonary hypertension was present or not. Focal changes, present in every case, included thrombotic obstruction of segmental arteries, infarction and abnormal arterial anastomoses These did not give rise to any important reduction in the pulmonary arterial bed

Diffuse changes were found only in those cases with pulmonary hypertension They were of two kinds One was widespread obstruction of arterioles and small arteries less than 0 2 mm in diameter. The other was a generalized, diffuse narrowing of the peripheral arteries and arterioles; their caliber being reduced to between two-thirds and one-half of the normal The bore of these arteries was usually smooth, but occasionally there were indents due to patchy arteriosclerosis The segmental arteries were constricted especially in the lower half of the lung

In a single case of *congenital heart disease* with a large left to right shunt and a normal pulmonary vascular resistance, the arteriogram showed dilatation of the pulmonary artery and its segmental branches; but the peripheral pattern was normal apart from areas of infarction.

In cases with pulmonary hypertension, the arteriogram showed widespread narrowing or occlusion of the smaller arteries and arterioles The size of artery affected varied In one case, the majority of arteries up to 2 0 mm in diameter were obstructed; in another, those below 0 4 mm.; and in a third, those below 0 2 mm

In each of the seven cases of *solitary pulmonary hypertension* there was a great reduction in the arterial bed, particularly at the level of the small arteries and arterioles In three cases, the narrowing chiefly affected arteries 0 4 to 0 7 mm in diameter; in two, arteries 0 1 to 0 3 mm ; and in one, the arterioles In the seventh case, there was simply a diffuse narrowing of the segmental arteries and all their branches right out to the periphery without significant occlusion

Summarizing thus far, then, we may say that pulmonary arteriography, performed in such a way that it demonstrates only *organic* narrowing, has invariably shown a great reduction in the pulmonary arterial bed in cases of established pulmonary hypertension.

Two distinct types of arterial narrowing have been revealed. One is occlusion, or abrupt stenosis of the lumen so great as to prevent the onward passage of the radio-opaque medium The site of maximum obstruction varied in different cases (fig 2) In recurrent pulmonary embolism, it was in arteries 1 0 to 10 mm in diameter or even larger. In congenital heart disease, it was in arteries 1 0 to 0 1 mm In solitary pulmonary hypertension, it was in arteries 0 8 down to 0 03 mm In mitral stenosis, it was in arteries 0 2 down to 0 03 mm The other type of narrowing is a diffuse reduction in caliber of the peripheral arteries to between two-thirds and one-half of the normal (fig 3). As a rule, the two types of narrowing were complementary, but occasionally, the diffuse form was found alone

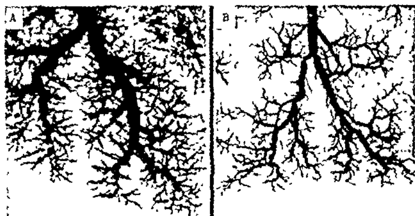



FIG. 4.—Magnified arteriogram, showing the degree of narrowing caused by arterial contracture.

A Arteriogram of normal lung lobule (x 5).

B Arteriogram of lung lobule in pulmonary hypertension, showing diffuse narrowing of arteries and arterioles (x 5)

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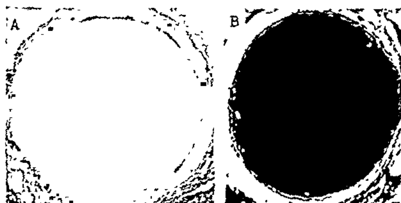



FIG. 5.—Histological sections of arteries in a state of contracture

A Elastic artery, approx 1 75 mm diameter (x 30)

B Muscular artery, approx 0.45 mm diameter (x 100)

The arteriograms of both the lungs from which these sections were taken showed a widespread, diffuse reduction of the arterial lumen to between one half and two thirds of the normal as in Fig. 4B

There is no intimal proliferation The arteries are fully distended by the bismuth suspension, as shown by the fact that the elastic laminae are smooth, they are, therefore, not in a state of spastic constriction. The narrowing of the lumen is not due to hypertrophy, since the wall accounts for only one tenth of the external diameter in A, and only one thirtieth in B

of variation in caliber, but it cannot be distended to the same degree as before. It gives the appearance of hypertrophy because the same amount of muscle is contained within a smaller circumference.

Poiseuille's law indicates that the pressure within a tube varies inversely with the *fourth* power of its radius. Admittedly, this law cannot be applied without qualification to the arterial circulation, but Burton *(1952)* has shown that it furnishes valuable approximations which are at least of the right order, provided the pressure is sufficiently above the critical closing pressure of the small vessels. Thus a small change in caliber has a profound effect on pressure. A reduction in caliber throughout the lung to two-thirds of the normal would raise the resistance approximately fivefold, while a reduction to half the normal caliber would raise the resistance sixteenfold.

*Correlation between Arteriographic and Histological Findings*

On histological examination, it was evident that the abrupt narrowing or occlusion was due to the presence of abnormal intimal tissue. In arteries over 1.0 mm. in diameter, this had the appearance of organized thrombus. In arteries less than 1.0 mm. in diameter its nature was frequently uncertain, and for this the term intimal proliferation is used. Intimal proliferation was often associated with focal medial thinning.

The nature of the diffuse arterial narrowing was not immediately obvious. The intima usually appeared normal. Sometimes the media seemed abnormally thick, but not always. The arteriographic appearances would be consistent with a spastic vasoconstriction persisting after death, but histological examination showed the arteries to be fully distended with their elastic laminae smooth and stretched. The narrowing is therefore organic and not spastic.

What is the nature of this organic change? Is it medial hypertrophy? As far as I am aware the presence of hypertrophy in the peripheral pulmonary arteries has never been established by direct measurement. O'Neal and others *(1955)* made careful measurements of the cross-sectional area of the media of the muscular pulmonary arteries in cases of mitral stenosis, and compared them with controls. They could not demonstrate any actual increase in media.

Furthermore, and this is crucial, the walls of the arteries in the injected lungs are not thick enough to account for the narrowing of the lumen which is seen in the arteriograms. If the lumen is narrowed by one-third, and this narrowing is due to mural hypertrophy, then the wall should account for at least one-third of the external diameter of the injected artery. In fact, it comes nowhere near to doing so (figs. 4 and 5). In segmental arteries the proportion is about one-tenth, and in muscular arteries about one-thirtieth. The diffuse arterial narrowing cannot therefore be due to medial hypertrophy.

The narrowing might be congenital. But then it is difficult to see why the media should appear thicker than normal. If it were a persistence of the fetal pattern as Edwards *(1950)* has suggested, it is difficult to see why it should be such a striking feature of an acquired condition like mitral stenosis.

It seems to me that we are forced to postulate a condition of acquired permanent contraction or arterial contracture (Short, *1957*). I suggest, though I know of no evidence as yet to support it, that when arteries remain in a state of tonic contraction for a certain length of time, their elastic and muscle fibers gradually become shortened without wasting. The artery remains capable

I think what Dr Dexter has shown us is a complication of pulmonary hypertension rather than a lesion that has caused pulmonary hypertension

HEATH I disagree strongly with Dr. Short as to the value of histological examination of the lung in cases of pulmonary hypertension and congenital heart disease. I believe pathology has much to offer in this field and of course one does not need to examine hundreds of sections, as he stated, to derive information about the effects of hypertension on the pulmonary vasculature One section from the pulmonary trunk and a section from each lobe of the lungs enables one to say whether the pulmonary hypertension in any given case is acquired or present from birth, and allows one to classify the changes into one of 6 grades, each of which has a precise relation to pulmonary artery blood pressure, flow and resistance. One also can make some deductions from histological examination as to the reversibility of the pulmonary hypertension While I believe Dr Short's use of arteriography gives an over-all picture and demonstrates vascular connections in the lungs, it cannot give the same precise detailed information to be obtained from histological examination of the lung

Let me use the example of Fallot's tetralogy to show how pathology enables one to predict what physiological conditions were present in life in the lung When the aortic configuration of elastica is present in the pulmonary trunk in this congenital abnormality, one can say that pulmonary hypertension was present from birth In these cases the muscular pulmonary arteries are thick-walled and the pulmonary arterioles have thick muscular walls These histological findings indicate that such a case of Fallot's tetralogy was of the "pink" acyanotic type with a high pulmonary blood flow and pulmonary hypertension

When the configuration of elastic tissue in the pulmonary trunk is of the chronic hypotensive type, the small muscular arteries are thin-walled and, like the pulmonary veins, contain thrombi These pathological findings indicate that this case of Fallot's tetralogy had a tight stenosis, with low pulmonary blood flow and pressure In short, it was of the classical cyanotic type

An intermediate form with normal pulmonary artery blood pressure and flow is indicated by an adult pulmonary configuration of elastic tissue in the pulmonary trunk, and normal muscular pulmonary arteries

I consider that few fields of pathology are so rewarding as this for there is a precise relationship between the physiological and pathological data

SPAIN Dr Short, I may have misunderstood but I thought you said that you used a pressure of 50 mg for normal lungs and 100 mg for the lungs with pulmonary hypertension It seems to me that if you used a different pressure for injecting this material, then the basis for a realistic comparison of the degrees of vascular narrowing in abnormals and normals does not exist

SHORT The pressures were arranged in such a way as to rule out the sort of difference that we have been speaking about That is to say, the lungs which showed the narrower arteries had been injected at a higher pressure

COMROE Physiological measurements are usually measurements made on the whole lung or on the whole pulmonary circulation or on large areas of it I am not sure that the section of the lung representing one very small part

## Discussion

Edwards: In atrial septal defect, a systematic study of the pulmonary vessels with serial sections—and I am of the opinion that a study of serial sections is essential—results in the division of the cases of atrial septal defect into two rather clear-cut groups depending on whether or not there is elevation of pulmonary pressure or pulmonary resistance, whichever term you prefer.

Among the cases we have studied (and they are not easy to come by, at least, from necropsy material) in which pulmonary pressure was not elevated but blood flow was increased, the small arterioles at the periphery of the lungs were characterized by lumens of fairly wide caliber As a rule no significant lesion is observed Some acellular fibrous thickening of the intima may be present and if it is not extensive it may very well be an age change

A study of the cases in which pulmonary resistance is elevated shows many segments of vessels containing focal lesions These lesions may be characterized by acellular fibrous proliferation of the intima which occludes the lumen

The intimal lesions commonly originate at the beginnings of arterioles and extend to the parent muscular artery

In many formations of this type the media of the parent artery will not be hypertrophied, in others, the media is hypertrophied. What does all of this mean? It is my opinion that the high flow associated with atrial septal defect is traumatic

This term is rather nonspecific, but it occurs to me that high flow involving small vessels in the periphery of the lung, vessels that have relatively little support from surrounding tissue, causes vibration; such vibrations, and perhaps the turbulence of the blood flowing through those vessels, are irritating to the lining and cause the lining to respond by development of proliferative lesions I am of the opinion that this is the first thing that happens This is the stage, I think, when increased resistance begins

The medial hypertrophy that does appear eventually may be a response to the elevated pressure that the increased intimal resistance has caused The medial hypertrophy may also be, in part, a response to peculiar transmissions of reflex pulse waves into the vessel

In Dr Dexter's photograph, there was a thrombus in a large pulmonary artery We recognize that such things can happen in atrial septal defect, but I think we have to recognize that they do not represent the beginning of pulmonary hypertension In atrial septal defect, when pulmonary hypertension is present, a complication of the pulmonary hypertension is disease of the major pulmonary arteries. The disease of the major pulmonary arteries is characterized by atherosclerosis of the large vessels, the elastic arteries The pulmonary hypertension alone, or the atherosclerosis which results from the pulmonary hypertension, coupled with the pulmonary hypertension, is responsible for formation of aneurysms in the large pulmonary arteries This is a complication not of atrial septal defect but of pulmonary hypertension It may complicate any type of pulmonary hypertension.

# Regression of Pulmonary Vascular Hypertension After Cure of Intracardiac Defects

*By* Howard B. Burchell

In the beginning, acknowledgment must be made to my many colleagues for their work represented in this communication, and in particular to the surgeons—Dr Kirklin, Dr Ellis, and Dr. McGoon—who carried out the curative surgery in the cases to be described The physiologic data have been made available to me by Drs. Wood, Swan, and Shepherd; and the help of Drs. Edwards, Heath, and Helmholz in correlating these data with the pathology is greatly appreciated

Pulmonary hypertension, as a manifestation of pulmonary vascular obstruction, is rarely benign, and when it is progressive one may well have forebodings concerning the patient's future. There are occasional exceptions to the expected unfavorable clinical course, in that some patients with cyanosis related to a right-to-left shunt at either the ventricular or a great-vessel location hold a plateau of very adequate capacity over many years

The implication of the title is that the abnormalities in the pulmonary circulation which result in pulmonary hypertension may regress after the basic intracardiac defect is remedied, and for a symposium it seems fitting to present one's own material primarily I can mention the reinforcement of scattered reports in current medical publications and also personal communications which coincide with the observations made at the Mayo Clinic; but even so, I must emphasize that data relating to this problem are indeed scanty The paucity of observations which are of sufficient duration to be useful is a limiting factor in prediction of the regression of pulmonary hypertension in surgical patients

Probably the reasons underlying the limitations of postoperative studies as compared to the number of patients operated upon are related to the following factors First, patients with the most advanced pulmonary vascular changes either are not chosen for surgical treatment or do not survive the surgical correction of the defect long enough for the theoretically possible regression to be observed Second, patients who are clinically cured, particularly children, are not readily subjected to postoperative cardiac catheterization; and often restudies are deferred until more opportune times when the patient will cheerfully undergo further investigative procedures Third, of the patients who are restudied there is biased selection Often those who appear to have either complete success or certain degrees of failure of the surgical procedure are chosen for study in order to settle key points in the physician's therapeutic rationale With such biased selection of patients for postoperative study, the data gathered cannot render trustworthy typical values for the total group

of a lung or even two or three such parts can give information which can be correlated with the physiological measurements made on the entire lung.

I would make a plea for using more ways of getting at the whole picture in every patient. whole lung sections, pulmonary angiograms, injected specimens plus removal of small bits of lung for microscopic examination.

DAMMANN: Perhaps the major argument against there being a congenital hyperplasia of the media as the explanation for the development of pulmonary vascular disease is that one can produce pulmonary vascular disease in the experimental animal by the creation of a large systemic artery-pulmonary artery anastomosis. This can be done in 100 per cent of animals.

pulmonary vascular resistance as calculated in the usual way. The patient appeared well and had no complaints at the time of the postoperative study.

The third case (table 3) shows oxygen reducing pulmonary resistance again, but 10½ months postoperatively a restudy did not indicate that the resistance to flow in the lungs had decreased. In the fourth case (table 4) the hemodynamic studies made preoperatively and 1 year postoperatively indicate no proof of regression in pulmonary resistance. It is particularly interesting that when this patient exercised (pedalling in the supine position) the pulmonary pressure increased by a factor of 2.6 but the flow increased by a factor of only 1.7.

TABLE 1.—*Atrial Septal Defect With Pulmonary Hypertension*
*Female Patient, 39 Years Old*

| Breathing | Pulmonary data | | | Systemic flow, L./min | Shunt, L.R., %* | Mean pressure, mm Hg | |
|---|---|---|---|---|---|---|---|
| | Pressure, mm Hg | Flow, L./min | Resistance, dynes sec cm $^{-5}$ | | | Right atrial | Wedge |
| | | | Preoperative | | | | |
| Air | 70/26 | 14.0 | 230 | 3.3 | 75 | 7 | 8 |
| Oxygen | 62/23 | 24.0 | 120 | 3.5 | 85 | — | 6 |
| | | | Postoperative (2 weeks) | | | | |
| Air | 45/22 | 4.0 | 600 | 4.0 | 0 | 1 | 8 |

* Percentage of pulmonary flow

TABLE 2.—*Atrial Septal Defect With Pulmonary Hypertension*
*Female Patient, 46 Years Old*

| Breathing | Pulmonary data | | | Systemic flow, L./min | Shunts, per cent | |
|---|---|---|---|---|---|---|
| | Pressure, mm Hg | Flow, L./min | Resistance, dynes sec cm $^{-5}$ | | R.L.* | L.R.† |
| | | | Preoperative | | | |
| Air | 66/22 | 7.0 | 420 | 3.9 | S‡ | 45 |
| Oxygen | 71/23 | 7.5 | 410 | 3.3 | S‡ | 55 |
| | | | Postoperative (4½ months) | | | |
| Air | 35/12 | 3.7 | 430 | 3.7 | 0 | 0 |
| Oxygen | 34/16 | 3.9 | 450 | 3.9 | 0 | 0 |

* Percentage of systemic flow
† Percentage of pulmonary flow
‡ S = slight

I assume general recognition that data pertaining to increases in pulmonary arterial pressure without parallel data on blood flow are not meaningful Let us focus our interest on the resistance offered to flow by the pulmonary vasculature, and on what proportion of this resistance may be related to organic change, reversible or irreversible, and what proportion dynamic factors, specifically vasomotion, may contribute

In the past decade when the surgeon made therapeutic excursions in the field of congenital heart disease and recorded his triumphs in the curative closure of the patent ductus and atrial septal defect, pulmonary hypertension was only occasionally a problem Indeed, in many cases with very high pulmonary flow and slightly elevated pulmonary arterial pressure the calculated resistances in the pulmonary vasculature were lower than normal. With the advance of the surgeon into the field of correction of ventricular septal defect, however, the problem of evaluating the significance of severe pulmonary hypertension has become an almost everyday problem, and the proper assessment of the state of the pulmonary vasculature is the central theme of discussions relating to operability and cure

The possibilities of regression of pulmonary vascular changes which, in association with congenital intracardiac shunt, produce pulmonary hypertension can be presented best through selected cases Each case may be regarded as a beachhead upon the formidable problem, where previously assaults of research have met with limited success and often failure

To indicate trends of the postoperative changes in the pulmonary circulation, I have chosen five cases of atrial septal defect, two of patent ductus, and two of ventricular septal defect From these examples one can make the definite suggestion that the most opportune times for restudy of patients who have had operations to remedy cardiac defects with associated pulmonary hypertension are early in the postoperative period and some years thereafter

### Atrial Septal Defect With Pulmonary Hypertension

It is of interest that in the early postoperative period following closure of an atrial septal defect the calculated pulmonary resistance may not decline, but actually increase In table 1 may be seen a decrease in pulmonary pressure and in pulmonary flow, but the calculated pulmonary resistance is considerably higher This case and others that Dr Swan of our group has studied suggest the possibility that in some instances the pulmonary vasculature "gives" or dilates in response to high pressure The enlarged lumina would offer less resistance to flow, and conversely, with lowering of pressure the lumina would narrow. Such observations made in a number of cases will be the topic of a more extensive separate report In the case here considered (table 1), the change in calculated resistance could not be attributed to any increase in left atrial pressure, as the wedge pressure showed no change In addition one may note that with the breathing of 100 per cent oxygen the pulmonary resistance decreased, and this phenomenon was repeated in the other cases to be represented in succeeding tables

In the second case (table 2), again it may be seen that the shunt was cured by surgery; but the passage of 4½ months brought no definite change in the

Again in the fifth case (table 5) it is evident that postoperatively the pulmonary vascular resistance did not significantly change In this patient, a man 40 years of age, the pulmonary flow seems to follow mean pressure within a certain range, in that with exercise the mean pulmonary pressure increased by a factor of 1 6 and the mean flow by a factor of 1 5

## Patent Ductus Arteriosus With Pulmonary Hypertension

Two cases have been chosen to illustrate the change in pulmonary hemodynamics after closure of a patent ductus arteriosus which had allowed left-to-right shunt despite associated pulmonary hypertension

In the first case (table 6) pulmonary vascular resistance appears to have

Table 6.—*Patent Ductus Arteriosus With Pulmonary Hypertension*
*Female Patient, 28 Years Old*

| Breathing and state | Pulmonary data: Pressure, mm Hg | Flow, L/min. | Resistance, dynes sec cm⁻⁵: Total | Arteriolar | Shunt, L R, per cent * |
|---|---|---|---|---|---|
| | | Preoperative | | | |
| Air during | | | | | |
| Rest | 83/52 | 10 3 | 450 | 380 | 60 |
| Exercise | 110/69 | 11 8 | — | — | 10 |
| Oxygen | 55/35 | 16+ | 210 | 155 | — |
| | | Postoperative (7 months) | | | |
| Air at rest | 38/14 | 8.5 | 190 | 133 | 0 |

* Percentage of pulmonary flow.

decreased. 7 months after operation the calculated resistance was within normal range in the presence of high cardiac output. It should be noted, however, that the postoperative value for pulmonary resistance is approximately the same as was obtained when the patient was breathing 100 per cent oxygen prior to operation

The longest postoperative follow-up in our clinic in a case of severe pulmonary hypertension associated with patent ductus arteriosus is that on a man whose ductus was closed in 1950 when he was 21 years of age (table 7) Preoperatively the pressures in the aorta and pulmonary artery were equal, the left-to-right shunt was only moderate, and the calculated pulmonary resistance was very high At that time the patient was markedly incapacitated and had been recently in heart failure. Ten months postoperatively, at which time he was feeling reasonably well and working full-time, he continued to have pulmonary hypertension and a rather low cardiac output, and the calculated vascular resistance remained high, despite reduction Seven and a half years after his operation there appeared to be still the same limit on cardiac output and almost the same high pulmonary vascular resistance. Notwithstanding these conditions, the pa-

TABLE 3.—*Atrial Septal Defect With Pulmonary Hypertension: Female Patient, 47 Years Old*

| Breathing | Pulmonary data | | | Systemic data | | Shunts, per cent | |
|---|---|---|---|---|---|---|---|
| | Pressure, mm. Hg | Flow, L./min. | Resistance, dynes sec. cm.$^{-5}$ | Flow, L./min | Resistance, dynes sec. cm$^{-5}$ | R L* | L R† |
| | | | Preoperative | | | | |
| Air | 100/37 | 5.7 | 810 | 3 5 | 119/57 | 13 | 45 |
| Oxygen | 90/30 | 8 5 | 550 | 3 0 | 118/58 | 0 | 68 |
| | | | Postoperative (10½ months) | | | | |
| Air | 50/27 | 4.1 | 680 | 4 1 | 119/49 | 0 | 0 |

* Percentage of systemic flow.
† Percentage of pulmonary flow.

TABLE 4.—*Atrial Septal Defect With Pulmonary Hypertension. Female Patient, 49 Years Old*

| Breathing and state | Pulmonary data | | | Systemic data | | Shunts, per cent | | Oxygen uptake, cc./min |
|---|---|---|---|---|---|---|---|---|
| | Pressure, mm Hg | Flow, L./min. | Resistance, dynes sec cm$^{-5}$ | Pressure, mm Hg | Flow, L./min. | R L* | L R† | |
| | | | Preoperative | | | | | |
| Air | 102/31 | 5 5 | 800 | 150/80 | 4.4 | 18 | 29 | 195 |
| Oxygen | 89/25 | 9.2 | 390 | 140/75 | 4 1 | 0 | 54 | 211 |
| | | | Postoperative (1 year) | | | | | |
| Air during | | | | | | | | |
| Rest | 32/14 | 4.0 | 400 | 164/79 | 3.7 | 0 | 0 | 193 |
| Exercise | 77/39 | 6.8 | 610 | 247/116 | 6 2 | 0 | 0 | 700 |

* Percentage of systemic flow.
† Percentage of pulmonary flow

TABLE 5.—*Atrial Septal Defect With Pulmonary Hypertension Male Patient, 40 Years Old*

| Breathing and state | Pulmonary data | | |
|---|---|---|---|
| | Pressure, mm Hg | Flow, L./min | Resistance, dynes sec cm$^{-5}$ |
| | | Preoperative | |
| Air | 65/20 | 6 3 | 560 |
| | | Postoperative (11 months) | |
| Air during | | | |
| Rest | 33/18 | 4 5 | 436 |
| Exercise | 57/27 | 6.7 | 448 |

ation by histologic study of pulmonary vasculature made available at operation to repair ventricular septal defect should be given close scrutiny by this conference It is my opinion that there is fair correlation between the extent of morphologic changes and the severity of the pulmonary hemodynamic fault However, among the group of cases of "borderline operability" in which surgical treatment would be desirable because of progressing vascular disease, it is unlikely that one could use a pulmonary biopsy to gain a final answer that would remain unchallenged.

Of particular interest are the data of one patient who died some months after operation from a cause unrelated to the intracardiac repair At the time the defect was closed the pulmonary artery pressure dropped to normal levels, and the immediate postoperative condition was good At necropsy the closure of the defect was found to be complete The pulmonary vascular changes noted presented a forbidding appearance if regarded as the measure in selection. No regression in a vascular change could be recognized as having occurred in the few months following the operation

Two cases of this category demonstrate marked improvement in the pulmonary pressure and suggestive change toward normal in the pulmonary vascular resistance

In the child (table 8) it is apparent that the postoperative pulmonary circulation is adequate despite a calculated resistance of 680 (dynes sec cm $^{-5}$), which is to be compared with the preoperative value of 1245 This child is clinically well.

TABLE 8.—*Ventricular Septal Defect With Pulmonary Hypertension Female Patient, 6 Years Old at Operation*

| Pulmonary data | | | Systemic data | | | Shunts, per cent | |
|---|---|---|---|---|---|---|---|
| Pressure, mm Hg | Flow, L./min. | Resistance, dynes sec cm $^{-5}$ | Pressure mm Hg | Flow, L./min | Saturation, per cent | R L* | L R † |
| | | | Preoperative (16 months) ‡ | | | | |
| 109/74 | 5 4 | 1250 | 122/67 | — | 92 | S§ | L¶ |
| | | | Postoperative (17 months) ‡ | | | | |
| 33/14 | 2 3 | 680 | 113/87 | 2 3 | 97 | 0 | 0 |

* Percentage of systemic flow
† Percentage of pulmonary flow
‡ Breathing air at rest
§ S = small
¶ L = large (from dye curves)

In the other patient (table 9) the pulmonary pressure was moderately reduced when measured 8 months after operation, and the pulmonary vascular resistance was reasonably low It should be emphasized that this patient had had a defect estimated as 5 by 3 cm in extent, and a huge left-to-right shunt, Preoperatively her systemic pressure had been low when taken at frequent

*Table 7.—Patent Ductus Arteriosus With Pulmonary Hypertension: Male Patient, 21 Years Old at Operation; Surface Area 1.71 sq. M.*

| Pulmonary data | | | Systemic data | | Shunts, per cent | | Oxygen uptake, cc/min |
|---|---|---|---|---|---|---|---|
| Pressure, mm Hg | Flow, L/min | Resistance, dynes sec. cm.$^{-5}$ | Pressure, mm Hg | Flow, L/min | R L* | L R† | |
| | | | Preoperative ‡ | | | | |
| 100/70 | 4.5 | 1390 | 100/70 | 3.0 | S§ | 33 | 253 |
| | | | Postoperative (10 months) ‡ | | | | |
| 56/20 | 4.1 | 800 | 129/73 | 3.1 | 0 | 0 | 268 |
| | | | Postoperative (7½ years) ‡ | | | | |
| 48/20 | 3.1 | 730 | 105/72 | 3.1 | 0 | 0 | 217 |

* Percentage of systemic flow
† Percentage of pulmonary flow
‡ Breathing air at rest
§ S = slight

tient had been able to work without significant difficulty, being troubled only with mild exertional dyspnea and fatigability. It is believed that this patient may have associated mitral valvular incompetence, but the only evidence of it is the presence of an apical systolic murmur.

### Ventricular Septal Defect With Pulmonary Hypertension

In cases of ventricular septal defect, the pulmonary arterial pressure, particularly the diastolic level, usually is found to be somewhat lower at operation than that recorded on preoperative cardiac catheterization. This is of special interest because often the left atrial pressure is markedly increased at the beginning of the operation before the correction itself is initiated, and is higher than one would have anticipated from the preoperative wedge determinations. If the case has been chosen properly for operation, the pulmonary arterial pressure following correction of the defect and restitution of the circulation through the heart is lower than before the closure of the defect. This is expected and is of good omen. However, it is doubtful whether the immediate effect of the repair on the pulmonary pressure can be projected with any assurance to indicate the ultimate regression in pressure. If operative data are to be valid the defect must indeed be closed and the cardiac output must be adequate. Assurance of these two conditions is supported by obtainment of normal dye-dilution curves. If the pulmonary pressure does not drop with repair of the defect one fears that the patient will not survive many days; but usually with the present method of selection individuals who would respond thus can be excluded preoperatively, as they typically do not have an increased pulmonary flow and a left-to-right shunt then.

The possibility of predicting the pulmonary blood pressure response to oper-

tients with pulmonary vascular changes related to intracardiac defects, no progression of the vascular changes following complete repair of the intracardiac defect has been observed to date Evidence in this particular field also is inadequate as yet, but at least the clinician may take hope when no obvious progression of the pulmonary vascular changes is found, even though it is known or suspected that pulmonary hypertension has persisted following the intracardiac repair.

## Discussion

Cournand: I should like to ask Dr. Burchell whether he has attempted, in these patients, to establish a relation with age I suspect that in the young age group, the pressure would tend to decrease as they grow up, whereas in the older age group such a tendency should not be observed

Burchell I do not have these data and I cannot answer the question. I suspect that the answer would be the opposite of what I thought it would be two or three years ago, when I thought that the younger age group might show more regression, but arguing from a few instances, it appears that this concept will not be universally true

Wood: There have been two interesting points brought out this afternoon. The first one was glossed over and I would like to ask if either Dr Dammann or Dr Dexter has the explanation

They both said that the defect did not function during the first few months of life, but did not say why I wonder why it doesn't, and what proof have you got that it doesn't? Do you know the explanation? Has it not to do with the relatively slow involution of the right ventricle?

The other point of great interest is Dr Short's second point, that there was a difference in the position of the vascular lesions in mitral and primary pulmonary hypertension on the one hand, and in the Eisenmenger group on the other, in the former I think the terminal muscular arteries or even arterioles were chiefly involved, whereas in the congenital group it was the larger arteries Is that right?

Then, supposing you have a drug that worked in one of them and not in the other Would it determine, in your view, the site of action of the drug? For example, suppose you gave a vasodilator in primary pulmonary hypertension and it always worked, and suppose you gave the same vasodilator to Eisenmenger's complex and it never worked. Would you assume that the drug acted on the arterioles and not on the muscular arteries?

Dexter I was quoting your statement of last night, Dr Wood, to the effect that there was no shunt at birth.

I know of no documented proof of it, but a diagnosis is never made in the early months of life There is no murmur The right ventricle is hypertrophied and is as thick as the left ventricle Therefore, there would be no opportunity, I should think, for shunting But to answer your question, I don't know of any proof I am sure Dr Dammann does, however!

Dammann: I do not have any specific information as to the size of the shunt right after birth I would expect that there is a small shunt present very shortly after birth, because of the difference in filling pressure between

TABLE 9.—*Ventricular Septal Defect With Pulmonary Hypertension. Female Patient, 34 Years Old*

| State | Pulmonary data | | | Systemic data | | Shunts, per cent | | Saturation, arterial oxygen, % |
|---|---|---|---|---|---|---|---|---|
| | Pressure, mm Hg | Flow, L./min | Resistance, dynes sec. cm.⁻⁵ | Pressure, mm Hg | Flow, L./min. | R-L* | L-R† | |
| | | | | Preoperative ‡ | | | | |
| Resting | 54/18 | — | — | 84/64 | — | S§ | L¶ | 94 |
| Exercising | | — | — | — | — | — | — | 88 |
| | | | | At Operation | | | | |
| Before repair | 66/0[rv] | — | — | 80/55[a] | — | — | — | — |
| After repair | 45/23[rv] | — | — | 85/54[a] | — | — | — | — |
| | | | | Postoperative (8 months) | | | | |
| Resting | 36/21 | 5 6 | 430 | 103/64 | 5 6 | 0 | 0 | 97 |

* Percentage of systemic flow
† Percentage of pulmonary flow
‡ Catheterization elsewhere, full data not available.
§ S = small.
¶ L = large.
rv = right ventricle
a = aorta

clinical observations, and a question is raised whether there may be an absolute *threshold of* blood pressure above which development of pulmonary vascular change is accelerated.

## COMMENT

The response of the pulmonary vascular bed to the breathing of 100 per cent oxygen gives useful information regarding the capabilities of pulmonary vascular circulation in the presence of severe pulmonary hypertension Probably the change of resistance with oxygen breathing gives valuable clues as to the operative result that may be obtained. Possibly it may indicate also what regression will occur in the pulmonary vascular obstruction

That assay of the pulmonary vasculature by the morphologist in the presence of *moderate* increases of pulmonary vascular resistance will accurately predict hemodynamic regression is doubtful One would expect quantitative correlation and possibly a qualitative correlation in respect to regression, the latter referring to whether primarily medial or intimal change predominates

Selected case studies indicate that when severe pulmonary vascular obstruction is demonstrated by high calculations of resistance (or high pressure/flow ratios) the return to normal should not be expected In pulmonary hypertension associated with ventricular septal defect or with patent ductus arteriosus the promise of regression may be greater in young patients, but this hope is based on clinical impressions, available exact data being inadequate In pa-

# VI. THE PULMONARY CIRCULATION IN ACQUIRED HEART DISEASE

CHAIRMAN: PAUL WOOD

CO-CHAIRMAN: EMMETT B. BAY

## The Occurrence and Significance of Increased Pulmonary Vascular Resistance

*By* LEWIS DEXTER

PULMONARY VASCULAR DISEASE implies an obstruction to blood flow through some part of the pulmonary vasculature What role the bronchial anastomotic circulation plays I do not know and therefore will not refer further to it. The obstruction may be in the main trunk of the pulmonary artery, its larger branches or its finer radicles. There may be an important obstruction at the level of the capillaries themselves as a result of a variety of diseases Little mention has been made at this conference of the histology of the capillaries or of their histological appearance That there can be great changes in capillary morphology, however, is well attested by the thickened alveolar-capillary membrane in mitral stenosis Little is known of resistance offered by the venules in disease processes and practically no mention has been made of these important structures in this conference Kuida et al[1] have recently demonstrated venular obstruction as a result of the administration of histamine and of E coli endotoxin. Pulmonary venous obstruction is apparently rare Dr Edwards[2] has referred to one case of congenital stenosis of these vessels and I have seen one case of narrowing of all the pulmonary veins by a granulomatous lesion, the syndrome resembling that of mitral stenosis except for the absence of a murmur and of an enlarged left atrium

Current methods allow for the localization of the resistance in the pulmonary vasculature by measurement of pressure differences in different parts of the circuit, i e, pulmonary artery, pulmonary "capillary" wedge (which current evidence appears to indicate is the pressure in the pulmonary capillary bed itself[3]) and left atrium Under most circumstances, left atrial and pulmonary "capillary" wedge pressures are essentially identical

One or more of the following mechanisms for reduction of the cross-sectional area of the pulmonary vascular bed may be operating in the development of increased pulmonary vascular resistance.

1. Destruction of the pulmonary parenchyma
2. Plugging of the vessels

the right and left ventricle due to the relative size of the tricuspid and mitral valves and the shape of the inflow tract of the ventricles The shunt, then, increases, because of thinning and dilatation of the right ventricle and because of relative thickening of the left ventricle.

SHORT Dr Evans and I showed that in mitral stenosis a sort of silting-up process occupied the arterioles and the smallest muscular arteries up to about 0 2 mm in diameter In congenital heart disease and in primary pulmonary hypertension the silting-up extends to the larger branches, up to 0 8 mm or even 2 0 mm.

From the point of view of drug action, I have felt that in mitral stenosis there is a greater length of vessel for the vasodilator to work on, and this might explain any difference in effectiveness

The idiopathic form of pulmonary vascular disease, so-called primary pulmonary hypertension, is rare and as its name implies, the etiology is unknown Its manifestations can be precisely simulated by recurrent pulmonary embolism, and in my own experience it should be considered as such during life.[6] A finite diagnosis necessitates autopsy confirmation The group of congenital heart diseases, of which atrial septal defect, ventricular septal defect and patent ductus arteriosus are the common and salient examples, there being others, were discussed yesterday in some detail Finally, lesions of the left side of the heart, particularly mitral stenosis and left ventricular failure from any cause, are characterized by an elevation of the left atrial, pulmonary venous and pulmonary capillary pressures and also by an exaggerated elevation of the pulmonary arterial pressure. Whether there is reflex constriction of the pulmonary arterioles as a result of elevation of pulmonary capillary or pulmonary venous pressure, or whether the progressive pulmonary vascular disease is initiated by the concomitant elevation of the pulmonary artery pressure is not known Dr Donald[7] will, I believe, go into this problem in detail.

I would now like to say a few words about the methodology in measuring resistance. Resistance is usually calculated as follows·

$$\text{Pulmonary Vascular Resistance} = \frac{\text{Pulmonary Artery Mean Pressure—Left Atrial Mean Pressure}}{\text{Cardiac Output}}$$

The shortcomings of this calculation have been emphasized in this conference On the other hand, the importance of measuring both pressure and flow and equating the two needs emphasis The calculation is valid The only difficulty is its interpretation.

There is a tremendous pulmonary vascular reserve The work of Gibbon, Hopkinson and Churchill[8] many years ago indicated that it was necessary to reduce the cross-sectional area of the pulmonary artery about two-thirds before any change in pressure or flow could be detected at rest or, in other words, before there was any change in calculated pulmonary vascular resistance Stated in another way, the finding of an increased pulmonary vascular resistance indicates an enormous reduction in the cross-sectional area of the pulmonary vasculature Dr Soderholm[9] has referred to the effect of unilateral pulmonary vascular obstruction in man, and the following two figures illustrate the effect in dogs[10] As will be seen in figure 1, there was little change in cardiac output. The right ventricular systolic pressure rose only slightly for a short period of time, systemic blood pressure was reduced insignificantly, the calculated pulmonary blood volume (cardiac output times mean transit time) was reduced on the average only 6 per cent (well within the error of the method), albeit about 50 per cent of the pulmonary vasculature had been occluded Indicator-dilution curves obtained before and after unilateral pulmonary arterial occlusion are illustrated in figure 2 Thus, sudden unilateral pulmonary arterial occlusion results in dilatation of the vessels of the unoccluded lung so that pressure, flow, and therefore calculated pulmonary vascular resistance remain essentially unchanged

So far in this conference, little has been said about the pressure-volume characteristics of the lung, i e, how much blood must be added to the lung

3. Organic narrowing of the vessels
4. Vasoconstriction

Pulmonary vascular disease may be classified in a variety of ways. The following, modified from Spain and Handler [3] and McMichael,[4] and others, represents one way of grouping the various lesions which predispose to pulmonary vascular disease:

*Classification of Pulmonary Vascular Disease*

1. *Acute*
    a) Pulmonary embolism
2. Subacute
    a) Miliary carcinomatosis
        1) Hematogenous dissemination
        2) Lymphatic dissemination
3 Chronic
    a) Diffuse pulmonary parenchymal disease
        1) Emphysema
            a. Obstructive
                Asthma
                Chronic infection, etc
            b Nonobstructive
                Senile
                Kyphoscoliosis, etc.
        2) Pulmonary fibrosis and granulomatosis
            a. Tuberculosis
            b Pneumonoconiosis (silicosis, etc.)
            c. Idiopathic (Hamman's disease)
    b) *Diffuse pulmonary vascular disease*
        1) Recurrent pulmonary embolism
        2) Thrombosis of pulmonary artery
        3) Sickle cell anemia
        4) Schistosomiasis
        5) Arteritis
            a *Thromboangiitis obliterans*
            b. Lupus erythematosus disseminata
            c Polyarteritis nodosa
        6) Idiopathic
    c) Congenital heart disease
        1) Atrial septal defect
        2) Ventricular septal defect
        3) Patent ductus arteriosus
    d) Lesions of the left side of the heart
        1) Mitral stenosis
        2) Left ventricular failure

Acute pulmonary embolism consists not only of mechanical plugging of the pulmonary vascular tree, but also there appears to be, from the work of Price et al ,[5] a far more important factor of vasoconstriction In the group of patients with diffuse pulmonary parenchymal disease, the most important principle is that they be diffuse and that large portions of the parenchyma be destroyed. These lesions are readily recognized by x-ray. In the diffuse pulmonary vascular diseases, again it is important that the vascular alterations be diffuse X-rays show no lesions to be present in the lung, the only abnormality being prominence of the pulmonary artery and of the hilar vasculature.

sites and all temporally equidistant points, i e , as usually performed between pulmonary artery and brachial artery, thus including the left side of the heart and large arteries in addition to the pulmonary blood volume itself If the normal volume between these points is about a liter and the error 15 to 20 per cent, it can be seen that a shift of 150 to 200 cc. of blood can occur in and out of the pulmonary circuit before detection This is a large volume of blood, the effects of which on the pressure-flow relationships within the lung would theoretically be considerable The only method which is currently more sensitive is to suspend the patient on a delicate balance to detect headward or footward shifts of blood.

Finally, a powerful vasodilator is needed for evaluating the rôle of vasoconstriction in the pulmonary vasculature Dr Fowler [12] has covered the present status of this subject. Perhaps priscoline is such a drug but I am not sure acetylcholine would appear to be a mild vasodilator

In summary, (1) in pulmonary vascular disease it is important to localize the area of high resistance in the pulmonary vasculature, and current methods suffice; (2) it is difficult to recognize pulmonary vascular disease by current methods until it is advanced, because of the large pulmonary vascular reserve, (3) the importance of a redistribution of blood into and out of the lung in altering pressure-flow relations and therefore calculated resistance has been emphasized; (4) the need of a powerful pulmonary vasodilator for assessing the rôle of pulmonary vasoconstriction is apparent

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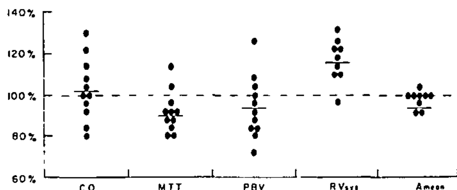
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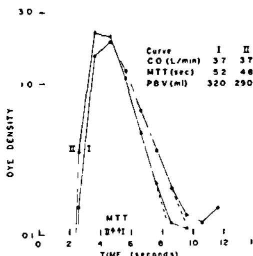




FIG 1 —(*top*) Hemodynamic changes following unilateral pulmonary arterial occlusion Unilateral pulmonary arterial occlusion in a closed chest dog was produced by a balloon on the end of a catheter Note the minor variations in the various circulatory parameters measured. The cardiac output (CO) and right ventricular systolic ($RV_{sys}$) and aortic mean ($A_{mean}$) pressures did not change importantly, the mean transit time (MTT) shortened, and the calculated pulmonary blood volume (PBV) between pulmonary artery and femoral artery remained essentially unchanged

FIG. 2 —(*bottom*) Indicator dilution curves before (I) and after (II) unilateral pulmonary arterial occlusion Note that the only important change was a reduction in the mean transit time (MTT), the cardiac output (CO) remaining unchanged and the calculated pulmonary blood volume (PBV) remaining well within the experimental error of the method

to effect a change in pressure-flow relations and therefore of calculated resistance. I have no data to present on this important parameter, but it has generally been neglected, particularly in pharmacologic studies of the human pulmonary vascular response to drugs, wherein redistribution of blood from lungs to periphery or periphery to lungs may have an important effect upon the apparent calculation of resistance (*vide infra*, Sarnoff [11]) Unfortunately, the indicator-dilution method for this measurement has an error of 15 to 20 per cent in measuring the volume of blood between injection and sampling

nary embolism itself, subacute repetitive thrombo-embolism, massive thrombosis complicating other disease affecting the pulmonary circulation such as atrial septal defect, and chronic multiple repetitive peripheral thrombosis complicating pulmonary hypertension from other causes. the first two examples illustrate pure obstructive pulmonary hypertension; the second two are polygenic.

*Obliterative pulmonary hypertension* may occur chiefly at the level of the capillaries, arterioles, or muscular arteries Capillary obliteration may, I am told, accompany emphysema and interstitial fibrosis, "endarteritis fibrosa," causing great thickening of the intima, appears to be the chief cause of occlusion of the arterioles and muscular arteries This group includes all forms of cor pulmonale in which the resistance is permanently high, schistosomiasis, disseminated lupus, periarteritis and perhaps primary pulmonary hypertension; it also complicates all other forms of pulmonary hypertension of sufficient duration just as organic vascular disease complicates essential hypertension in the systemic circulation

*Vasoconstrictive pulmonary hypertension* occurs in response to acute alveolar hypoxia, as first demonstrated by Liljestrand (*1918*). It certainly plays an important role when acute respiratory infections or bronchospasms complicate chronic cor pulmonale. It probably plays an equally important role in neonatal asphyxia, when it may well prevent the rapid decline in pulmonary vascular resistance that should take place after birth.

The most fundamental problem concerning the pulmonary circulation, however, is whether pulmonary vasoconstriction occurs in all other forms of pulmonary hypertension, however initiated, and if so whether it represents a response to the various agents that have been shown to cause or encourage pulmonary hypertension, or whether it represents a fundamental reaction to a raised tension within the pulmonary arteries themselves (elastic arteries, muscular arteries or arterioles) This problem will be taken up later.

*Polygenic pulmonary hypertension* is best illustrated by cor pulmonale, when hyperkinetic, obliterative, and hypoxic vasoconstrictive factors may all operate together The Eisenmenger group frequently shows both obliterative and obstructive (thrombotic) lesions in association with a strong potential hyperkinetic factor. But almost any form of pulmonary hypertension may become polygenic, particularly if it is shown that vasoconstriction results from pulmonary hypertension itself

## Conclusion

The initial cause of chronic pulmonary hypertension in any particular case is usually clear Primary pulmonary hypertension alone is obscure. Once initiated, pulmonary hypertention is maintained by the original cause (if it persists, as it usually does), and aggravated, possibly by reactive vasoconstriction, and certainly by organic occlusive changes in the pulmonary vasculature Evidence will be given later which suggests that the agent initiating pulmonary hypertension is rarely powerful enough to cause sufficiently high pressure to bring about organic occlusive vascular disease, and that the necessary accelerating factor is provided by reactive pulmonary vasoconstriction

## Chairman's Remarks

Chairman Wood: Dr. Dexter started with a classification, so I would like to discuss that first I have been a little disturbed during the conference with certain terms which do not mean the same to me as they do to the person using them. It always helps if we can find the right words to express exactly what we are talking about; otherwise there is apt to be needless misunderstanding For some years now at the Institute of Cardiology we have adopted the following classification, which may serve as well as another as a basis from which to arrive at the best nomenclature, and I offer it in that spirit

Table 1.—*Classification of Pulmonary Hypertension*

| Type | Definition |
|---|---|
| Passive | Elevated pulmonary venous pressure |
| Hyperkinetic | Increased pulmonary blood flow |
| Obstructive | Pulmonary embolism or thrombosis |
| Obliterative | Reduction of pulmonary vascular capacity |
| Vasoconstrictive | Functional vasoconstrictive reaction |
| Polygenic | Arising in more than one of the above ways |

*Passive pulmonary hypertension* may be caused by left ventricular failure, mitral stenosis, mitral incompetence, myxoma of the left atrium, cor triatriatum, and multiple pulmonary venous thrombosis; also to some extent by constrictive pericarditis and tense pericardial effusion.

*Hyperkinetic pulmonary hypertension* can only occur if the pulmonary vascular resistance fails to drop in response to increased flow

With a resistance of 0 5 units (40 dynes sec /cm $^5$), for example, a pulmonary blood flow of 30 liters per minute would not raise the mean pulmonary blood pressure above 20 mm Hg with a left atrial pressure of 5 mm Hg Hyperkinetic pulmonary hypertension therefore implies at least a high normal resistance of approximately 2 units; a 30 liter flow would then cause a pressure in the region of 80/40 mm Hg

Hyperkinetic pulmonary hypertension may occur in patent ductus, aortopulmonary septal defect, ventricular septal defect, perforated ventricular septum, atrial septal defect, perforation of the aortic sinus into the pulmonary artery, right ventricle or right atrium, and partial anomalous pulmonary venous drainage; associated with central cyanosis it may occur in transposition of the great vessels, persistent truncus, single ventricle, single atrium, and total anomalous pulmonary venous drainage directly or indirectly into the right atrium In acquired hyperkinetic circulatory states, such as thyrotoxicosis, anaemia, beri-beri, Paget's disease of bone and arteriovenous fistula, the pulmonary blood flow is rarely large enough to cause pulmonary hypertension; but when the cardiac output is increased in cor pulmonale, high pressures may be attained because the pulmonary vascular resistance is also raised. This, however, may be more properly regarded as polygenic pulmonary hypertension

*Obstructive pulmonary hypertension* may result from massive or multiple embolism or thrombosis. The most important examples include massive pulmo-

# The Effect of Experimentally Induced Hypervolemia on the Cardiac Function in Normal Individuals and Patients with Acquired Heart Disease

*By* LARS WERKO

THE CARDIAC OUTPUT in patients with mitral stenosis may be low even if no signs of myocardial failure can be demonstrated This is especially the case if atrial fibrillation is present. In some of these patients physical exercise may increase the output, usually with increasing pulmonary hypertension, but in others the ability to increase the output during exercise is compromised In an attempt to study more closely the factors regulating the cardiac output in mitral stenosis the effect of acutely induced hypervolemia was investigated For comparison similar studies were performed in normal individuals and patients with arterial hypertension

The results obtained when an isotonic solution of dextran was infused rapidly have allowed an analysis of the relationship between right heart filling pressures and cardiac output or right ventricular work The present report covers the results obtained regarding cardiac performance in 20 normal individuals and in 25 patients with heart disease, 15 of whom had mitral stenosis

Twenty normal volunteers, who were either members of the police force, medical students or nurses, were studied None of them had any history of renal or heart disease, nor did physical examination reveal any signs of such They were all studied on an ambulatory basis, resting for about an hour before and after the study.

The patients consisted of seven with arterial hypertension, three with aortic valvular disease and 15 with mitral stenosis The majority was only moderately limited by their heart disease and was classified functionally in group I or II according to the criteria of the American Heart Association Two patients had more symptoms and were classified in group III One patient had atrial fibrillation, all the others sinus rhythm

All studies were performed in the morning with the subject recumbent and in a postabsorptive state The pulmonary artery was catheterized and an indwelling needle placed in the brachial artery In about 50 per cent of the studies a double lumen catheter was used Cardiac output was determined according to the direct Fick principle and blood pressures recorded with a strain gauge manometer Blood samples for hemoglobin determination were ob-

*The work described in this paper has been carried out by a team consisting of B Thomasson, Truman G. Schnabel, Jr, Harold Eliasch and Edvardas Varnauskas*

## Discussion

Edwards: Dr Wood, you said the vasoconstrictive type of pulmonary hypertension *speaks for itself* I wonder if you would speak for it, too

Chairman Wood I was discussing a title. What I meant was that vasoconstrictive hypertension is due to vasoconstriction That is what I meant by it speaking for itself

I don't mean I knew that (a) it occurred or, (b) how it occurred, or anything about it I will be glad to discuss it in greater detail later on

Dawes Yesterday and the day before, various speakers implied that the pressure-flow *curve of the lungs is nonlinear at high rates of flow Do you know* of any evidence in human perfused lungs to substantiate this hypothesis, in conditions in which the effects of the nervous system are excluded?

Dexter No, I don't have any reason to think that there is any As a matter of fact, the evidence indicates that the pressure-flow relationship in the lung is not linear, that it is a curve, whereas the resistance formula (pressure difference divided by flow) is mathematically a linear expression In making the calculation of resistance, one assumes linearity but linearity exists only on one small part of the curve and I don't know where it is in the individual case

In trying to translate pressure-flow information into resistance, great difficulty is encountered when the changes are small With large changes, one is on firmer ground

Dawes May I put a supplementary question?

In mitral stenosis left atrial pressure rises Now in the middle of the pressure-flow curve all physiologists agree that in the isolated perfused lungs of animals the pressure-flow relationship is linear Consequently one might expect that, at an intermediate rate of blood flow, a small rise of left atrial pressure would lead to an exactly equal rise in pulmonary arterial pressure Yet in mitral stenosis a rise of left atrial pressure, you say, precedes and leads to gross pulmonary hypertension How does this come about?

The point that I wanted to establish is that you think there is an unknown factor which causes a rise of pulmonary arterial pressure out of all proportion *to that which was expected*

Dexter It seems to me that there are a couple of things here which have to be brought in

First of all, it is quite true that when the pulmonary venous pressure rises, the pulmonary arterial pressure rises proportionally so that the difference between the two remains essentially the same

In the chronic state of affairs, a change occurs wherein the pulmonary arterial pressure rises to high values, far beyond that occasioned by the rise of pulmonary venous pressure directly As to why this occurs, I don't think that the answer is entirely known Even under these circumstances of raised pulmonary vascular resistance, there is no particular change in the calculated resistance during exercise—sometimes it rises and sometimes it falls, but on the average, the resistance remains unchanged

mean pressure and pulmonary arterial mean pressure but with constant cardiac output.

When all the normal subjects are taken into consideration, an increase of blood volume of 20 to 35 per cent corresponded to an increase of right atrial mean pressure of 2 to 12 mm.Hg and pulmonary arterial mean pressure of 3 to 15 mm Hg. With the greatest expansion in blood volume cardiac and stroke output were increased 31 per cent and 20 per cent respectively In seven subjects, however, increases of right heart filling pressure of 4 to 12 mm.Hg were associated with changes in cardiac output of less than 15 per cent

When the right heart filling pressure was plotted against stroke volume, cardiac output or right ventricular work a variable relation was obtained In some cases the output increased with increasing expansion of plasma volume and increasing atrial pressure, in others the blood flow was constant When right ventricular stroke work was plotted against filling pressure the same variable relation could be demonstrated (fig. 2) It is important to stress that no change in oxygen consumption, heart rate or brachial arterial pressure occurred throughout the study

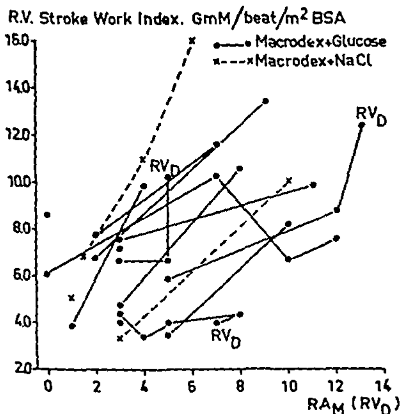



Fig 2.—Relation between the right heart filling pressure and right ventricular stroke work in normal individuals

tained periodically from the arterial needle. The percentage decrease in hemoglobin was used an an indication of the increase in blood volume.

Basal values were obtained when the subject had rested for about half an hour after the catheter had been placed in the pulmonary artery. In most cases two basal determinations of the cardiac output were done, one to two minutes apart Immediately after this, 6 per cent Dextran solution was given by a motor driven syringe, constantly injecting about 25 ml /min., through a small polyvinyl catheter into a cubital vein To the normals Dextran was given for about 60 minutes. The patients received the infusion for 30 to 50 min The infusion was interrupted when the pulmonary arterial pressure rose rapidly.

Determinations of cardiac output using the Fick principle and blood pressures were made repeatedly during the infusion and in some cases afterwards

*Results*

A typical study in a normal individual is shown in figure 1 With the infusion the blood volume increases progressively, with increases in right atrial

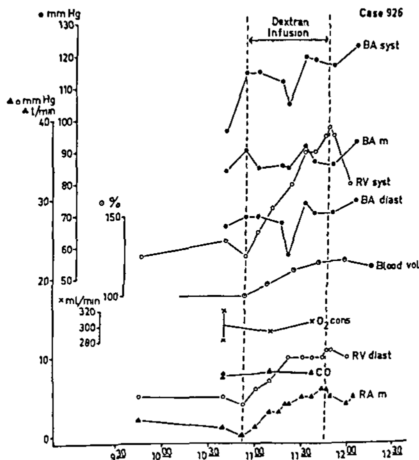



Fig 1—The effect of Dextran infusion on several physiological functions in the normal individual

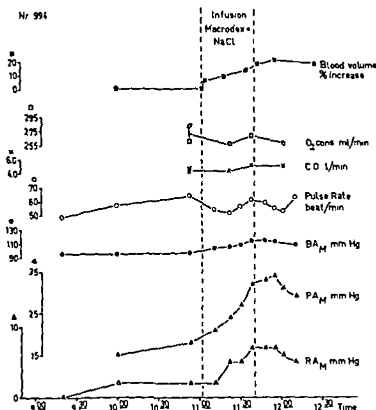



Fig 4 —The effect of Dextran infusion in a patient with mitral valve disease

crease in right heart filling pressure and the percentage change in cardiac and stroke output or the change in right ventricular stroke work

Increasing the blood volume rapidly in normal volunteers or in patients with arterial hypertension, mitral valvular disease or aortic valvular disease thus causes a rapid increase in right atrial and pulmonary arterial blood pressure and a variable increase in cardiac output The absence of correlation between changes in right heart filling pressures and changes in cardiac output or right ventricular work indicate that changes in filling pressures of the right heart do not regulate the cardiac output in the intact human being

In this study we have tried to correlate the right atrial pressure as representing the right heart filling pressure to the right ventricular work or cardiac output This was done because it is impossible to determine the diastolic volume of the ventricle in the intact human being and because several workers have transformed the original Starling Law of the heart to a relation between filling pressure, instead of diastolic volume, and ventricular output and work In open chest dogs Sarnoff and Berglund and co-workers have constructed modified Starling curves with rather large changes in ventricular work for small changes in filling pressures In studies in patients, decreasing filling pressure—with orthostatic changes, or during pressure breathing or acute blood

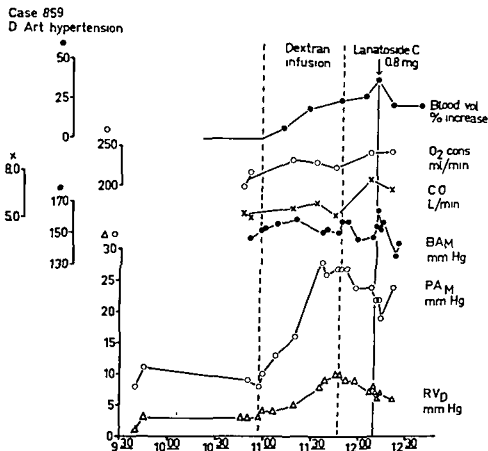



Fig 3 —The effect of Dextran infusion in a patient with hypertension

Similar results were obtained in the patients with heart disease A representative study in a patient with arterial hypertension is shown in figure 3 The right heart pressures increase uniformly without change in cardiac output or brachial arterial pressure In the patients with mitral valvular disease the pressure in the pulmonary artery increased more rapidly and more markedly than in the normals for the same increase in plasma volume and right atrial pressure (fig 4) This is presumably due to the changes in the pulmonary vascular bed known to occur in these patients

In the patients the same variable relation was found as in the normals between right heart filling pressure and cardiac output, stroke volume or right ventricular work The cardiac output increased sometimes but not always with the expansion of plasma volume In some patients a marked increase of right ventricular work occurred, in others the right ventricular work was almost constant. These patients who were all well compensated and with only slight symptoms, thus reacted almost exactly as the normals

While the data for the entire study support a conclusion that a rise in stroke and cardiac output occurs with increasing right heart filling pressures no uniform way of relating these variables was found Statistical treatment showed that no significant relation existed between the magnitude of the in-

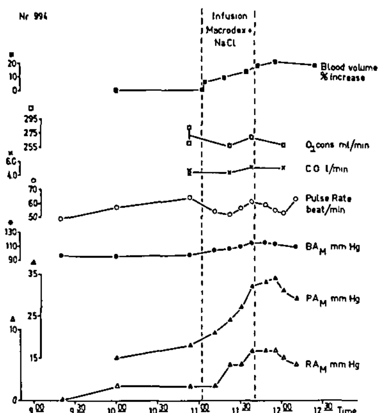



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loss—has been followed by decreasing output. From this it has been concluded that the filling pressure of a ventricle may play a role in regulating cardiac output However, recent work in the intact dog with increasing blood volume and filling pressures led to the same result as in the present study, that the increased cardiac output during such an experiment was related to other factors than the atrial pressure (Fowler, French and Bloom). Similar results have also been obtained by Fleming and Bloom in patients without cardiovascular disease

Besides increasing blood volume and elevating right heart filling pressure an infusion of Dextran causes other physiologic changes, which in themselves may play some role in the regulation of cardiac output Increased cardiac output found in dogs during dextran infusion was shown to be the result of a marked anemia In the present study the anemia was never of a magnitude comparable to that in those animal studies The hemoglobin concentration was never below 10 Gm per 100 ml. blood In patients with chronic anemia similar hemoglobin values never gave an increase in total blood flow.

During the infusion of Dextran the renal blood flow usually increased markedly, sometimes to twice the starting value This could not be due solely to the increase in cardiac output, but the increase in cardiac output could be due to a peripheral vasodilatation following the expansion of blood volume not only in the renal vascular bed but throughout the body. This hypothesis is supported by the fact that there was a statistically significant, albeit small, correlation between the increase in blood volume and increase in cardiac output or right ventricular work

The present study indicates that changes of right heart filling pressures seldom regulate right ventricular work or cardiac output. In a series of 15 patients with mitral stenosis where one catheter was placed in the right atrium and one in the pulmonary artery the reaction to 15 minutes of exercise was studied with almost continuous recording of pressures The relation between right ventricular work and filling pressure in these patients is shown in figure 5 They are divided in two groups those in groups I-II of the N Y Heart Association and those in groups III-IV, the latter in failure or close to it

The graph shows that during exercise right ventricular work increased (as did the cardiac output) without change in filling pressure in the former group In the latter group, on the contrary, right atrial pressure increased with increasing, unaltered or decreasing cardiac work When all data are taken into consideration, a curve similar to the Starling curve of Sarnoff and Berglund might be constructed Similar results have been obtained regarding the left ventricle in patients with arterial hypertension by our group and by Donald and co-workers

This indicates that only when the patient is close to failure the filling pressure increases when there is a demand for increased blood flow In the intact normal individual or in patients with heart disease not in failure other factors, notably nervous or humoral, are of greater importance for the regulation of cardiac performance than right heart filling pressures

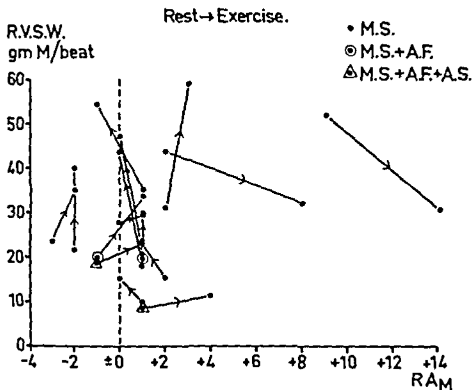



Fig 5 —The effect of exercise in the relationship between right ventricular filling pressure and right ventricular stroke work in 15 patients with mitral stenosis

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## DISCUSSION

SARNOFF This is of some interest to me and I appreciate having the opportunity to discuss this paper I think it is important to emphasize that on no occasion have either my colleagues or I, to the best of my knowledge, ever implied that filling pressure controls cardiac output or, in point of fact, that this has a determinant role in such control What we have attempted to do is simply to characterize the performance of the ventricle in response to changes in its filling pressure

Control of cardiac output, I am convinced, emanates from places different from the filling pressure of the heart. It has to do with the metabolic requirements of the organism On the other hand, this performance characteristic of the heart, namely its response to changes in filling pressure, is one of the important and responsive means *exploited* by the organism in the control of cardiac output.

There is one piece of information, lacking at the present time, which would make it possible to make a plausible interpretation of much of the data shown

by Dr. Werkö; that is, the displacement of the ventricular function curve from left to right, that is from an elevated to a less elevated curve as a result of the diminished activity of the cardiac sympathetic nerves and a consequent decreased liberation of myocardial norepinephrine during the period of induced hypervolemia While this has not been experimentally demonstrated, such a phenomenon would be consonant with what we now *think* we know about the control of cardiac output. Direct experimental observations about the effect of direct cardiac sympathetic nerve activity on the ventricular function curve are, I believe, important to obtain and we plan to attempt this shortly

I should like firmly to resist the notion that the heart is operating on a so-called ventricular function curve only when it is failing It is simply, I believe, that it may at such times no longer be as susceptible to influences which make it skip from one curve to another and thus data which fit a convincing curve are more readily obtainable without an especially thorough examination of the many operating parameters Further, it is but necessary to ask yourself a single question, originally pointed out to me by Dr. Carleton Chapman In what other manner can we explain the self evident fact that from minute to minute, week to week and year to year, the ratio of pulmonary to total blood volume is constrained within such relatively narrow limits? Were it not for the *continuing* operation of Starling's law the output of one ventricle would soon be dissociated from the output of the other and the lungs would soon be either almost dry or inundated (see E Berglund Ventricular function VI. Balance of left and right ventricular output: relation between left and right atrial pressures Am J Physiol *178*:381, 1954) Are we to believe that there are separate neuronal or humoral pathways for the individual control of each ventricle prompting them to keep pace so elegantly with each other? No evidence is at hand nor, to the best of my knowledge, has anyone had the temerity to suggest that the organism conducts its affairs in such a complicated and cumbersome manner

Mr. Chairman, I think the resolution, or at least partial resolution of this matter is the differing manner in which different investigators approach it If one demands, as was uniformly the case in yesteryear, that there be only one curve describing the relationship between filling pressure (or even fiber length) and stroke work, then such a person should scrap the whole affair; it will never be of any use to him If, however, "Starling's Law of the Heart" now be made to include the numerous families of curves describing this relationship, one can, I believe, extract a substantially augmented understanding of the heart's compensatory range precisely because studying those mechanisms, such as reflex effects on the heart, may well yield information as to which influences *will* shift the heart from one function curve to another.

WERKO: I know you are very fond of the ventricular function curve, and I also know you can explain almost everything by using a family of curves which shift direction according to other influences I didn't imply that you have said that the right atrial filling pressure regulated the cardiac output, but some of your co-workers and many other people have said it

You did however say that the different output of the right and left heart was due to the filling pressure of the right and left heart, shown by Berglund

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# Some Physiologic Considerations in the Genesis of Acute Pulmonary Edema

*By* Stanley J. Sarnoff

When our distinguished chairman, Dr Paul Wood, invited me to participate in this symposium and speak on hypertensive pulmonary edema I responded with enthusiasm In addition to a durable interest in the subject, this invitation provided me with the stimulus to reconsider the position which my colleagues and I had assumed a few years ago at the end of a period of aggressive experimental effort and also to attempt to integrate into that position the results of a variety of experimental experiences acquired since that time.

This brief presentation will treat with (1) the role of the heart itself, (2) the role of the peripheral vascular bed in the genesis of lung edema, and (3) an attempt to indicate which portions of the peripheral vascular bed are involved and in what manner It is well to stress at the very outset that whereas changes in arteriolar distensibility serve primarily a resistance function, changes in venous pressure-volume relationships serve primarily a volume function Later on I will touch briefly on the problem of the absence of lung edema in the presence of left atrial pressures which are elevated to a level substantially above that of the oncotic pressure of the blood

In *1878* Welch [1] fathered what is currently referred to as the Welch hypothesis, namely, that acute hypertensive lung edema is attributable to an increased resistance to the ejection of blood from the left ventricle and the consequent accumulation of blood in the lung Acute lung edema in the rabbit was readily observed after occlusion or stenosis of the aorta This hypothesis is still held by many people adequately to account, by itself, for the hypertensive lung edema syndrome In the same year, *1878*, Waller [2] made similar types of observations but in addition drew significant deductions about the transfer of blood from the systemic to the pulmonary circuit [3]

My own interest in this area was triggered in *1912*, while still a medical student, during observations on an elderly hypertensive gentleman who was in pulmonary edema but was nevertheless being prepared for the emergency removal of a badly strangulated scrotal hernia The patient's eventual recovery was quite naturally, attributed by the surgeon to the operative procedure I had little doubt however, that this patient's lung edema had all but completely resolved, as evidenced by auscultatory signs and his tolerance for the horizontal position in a very few minutes after the administration of the spinal anesthesia and well before the beginning of the surgical intervention The next year my good friend, Dr Hollon W Farr, a fellow interne at Bellevue Hospital and I administered spinal anesthesia to four patients in

*That implies that the right heart's filling pressure regulates output, doesn't it?*

SARNOFF: No Not in the slightest. What it does imply is that when the blood tends to maldistribute between the pulmonary and the systemic circulation, the result is a larger elevation of pressure in that circulation tending to receive the larger volume of blood At such a time, the continuing operation of Starling's law (on that point on that curve which obtains at that time) is the only known mechanism for regaining the proper distribution of blood volumes between lung and periphery Can you suggest any other?

KATZ A separate symposium should be planned to discuss the laws that regulate the performance of the heart.

I would like to direct a question to Dr Werko in relation to the pulmonary circulation What is the cause of the pulmonary pressure rise that you found when you gave these infusions?

WERKÖ The only explanation for the pressure rise that I can give is the increase in blood volume in the pulmonary vascular bed, because during this infusion you increase the total blood volume, and if it is distributed between the pulmonary and total circulation, which is reasonable, there must be an increase in the pulmonary blood volume That is the only explanation I have for the increased pressure

SHEPHERD Is Dr Werko prepared to commit himself as to whether he thinks the dextran infusion causes constriction of the pulmonary vessels in patients with mitral stenosis?

WERKO No

COURNAND. Should the viscosity of the solution injected be considered as a possible factor in these results?

WERKO The viscosity of the solution which is infused is slightly less than that of the plasma, and as you get hemodilution, the viscosity could not increase in the blood

DEXTER *May I ask a question? There was a rise of pressures in the pulmonary circuit as well as in the peripheral circuit;* there was an increase in calculated pulmonary vascular resistance, at least the pressure went up more than the flow Fluid had been added to both circuits Did you measure the pulmonary blood volume, and what effect do you think a change in pulmonary blood volume would have on the calculation of pulmonary *vascular* resistance?

WERKO We haven't measured the blood volume It was complicated enough as it was

therapy, if any, has not as yet been adequately investigated in other clinical types of lung edema.

5. Since, in these experiments, the arterial pressure was elevated and, where observable, the arterial tree appeared grossly enlarged, it seemed highly unlikely that the arterial bed contributed to the observed acute increase in pulmonary blood volume when this occurred after vasomotor center stimulation Potential changes in arteriolar volume were not thought to be sufficient to even nearly account for the changes By inferential exclusion, therefore, it was suspected that neuronally induced changes in systemic venous distensibility * played a major role in the observed augmentation of pulmonary blood volume That is to say, by their induced reluctance, as it were, to contain as much blood as they previously did at any given pressure, the systemic veins obliged the more passive pulmonary bed to accept a further complement of blood This view received support from the observations that a controlled, modest infusion (10 ml /Kg of saline in one minute) in the dog will normally produce only a slightly observable rise in left atrial pressure whereas the same intervention will cause a marked elevation of this pressure after peripheral vasoconstriction had been induced [7]

In the last analysis, however, my colleagues and I were not entirely comfortable about resting upon inferential exclusion as a satisfactory basis for understanding what we believed to be an important aspect of the pulmonary edema syndrome and I will return to a description of more recent experiments on changes in venous tone which, albeit of a preliminary nature, may shed additional light on this problem It is, however, necessary to introduce here a brief digression in the form of treating with the problem of what role the heart plays in all this

It would be unwise, to put it mildly, for me to deny that an increased resistance to left ventricular ejection will, by increasing the stroke work of that chamber, be accompanied by an elevation of the effective left ventricular filling pressure provided, of course, that neurohumoral influences have not induced a skip from the function curve on which the ventricle was originally operating In fact, my colleagues and I have spent the last five years in underscoring and attempting to interpret the significance of precisely this type of relationship [11-15] Such an increase in filling pressure is obviously also felt by the pulmonary vascular bed with which the left ventricle is in direct continuity during diastole and is therefore pertinent to our subject The plot between the ventricle's filling pressure and its stroke work is termed a modified Starling or ventricular function curve as seen in figure 1, a figure I show here with the kind permission of Dr Marion Cotten from whose article with Stopp [16] it has been reproduced It was purposely selected for presentation before this group because, in addition to showing the general shape of the left ventricular function curve it also contains information our own work did not include, namely the increased work that will be done from any given filling pressure under the influence of the glycosides, in this instance ouabain If, as was apparently the case from scrutinizing the data

* Used here in the physiological and not in the strictly physical sense

acute lung edema (but not in need of surgery) and were pleased to observe that they too benefited from this procedure.[4] Seven years later, Mrs. Sarnoff and I had the very great pleasure and the good fortune to join with Dr. Erik Berglund in a collaborative experimental attempt to understand what role, if any, the autonomic nervous system might play in the lung edema syndrome

It was observed, as had been described in detail by Cameron and De,[5,6] that diffuse chemical stimulation of the vasomotor center consistently produced hypertension and lethal lung edema in the rabbit. We could not agree with these authors, however, that the edema was attributable to a neuronally altered pulmonary capillary permeability since, when we measured left atrial pressures, these were found to be strikingly elevated Happily, the dog also yielded a similar response (although not as consistently) and thus made possible a somewhat more refined hemodynamic analysis than had been possible in the rabbit.[7,8] Experiments were done in which vena caval, pulmonary arterial, left atrial and aortic pressures were measured, and cardiac output continuously recorded along with changes in pulmonary blood volume, the latter being recorded by continually weighing the lungs during the course of the experiment [7,8] From these data, as well as from subsequent isolated perfused lung experiments,[9] it was possible to derive the general contour of pressure-volume relationships in the pulmonary vascular bed The upward convexity of this curve [3,9] when pressure is plotted on the vertical axis is of primary importance for the understanding of why only slight systemic vessel dilation can accomplish great reductions in pulmonary capillary pressures when the latter are initially elevated

The net sum of our position at the end of these experiments was the following.

1 *Stimulation of the vasomotor center (to which, it should be emphasized,* the cerebral cortex has access) promptly produces systemic arterial and venous hypertension, tachycardia, an increased peripheral vascular resistance and, of primary importance, markedly elevated pulmonary arterial and venous pressures consequent to an augmented pulmonary blood volume which, in *turn, is due to a substantial redistribution of blood from the peripheral vessels* to the pulmonary vascular bed

2 These changes are not dependent, or at least not primarily dependent upon nervous impulses to the lung since they are also observed after complete pulmonary denervation

3 The observed changes are readily reversible by means of ganglionic blockade It is of particular interest from the clinical as well as the theoretical point of view that a striking decrease of all pulmonary vascular pressures can be accomplished with only a modest degree of peripheral vasodilation insofar as this is indicated by a change in arterial pressure This, as indicated above, becomes understandable when related to the pressure-volume curve of the pulmonary vascular bed.

4. These laboratory observations have direct applicability to the clinical hypertensive pulmonary edema syndrome [10] as indicated by the prompt therapeutic response of such patients to ganglionic blockade The value of such

therapy, if any, has not as yet been adequately investigated in other clinical types of lung edema.

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It would be unwise, to put it mildly, for me to deny that an increased resistance to left ventricular ejection will, by increasing the stroke work of that chamber, be accompanied by an elevation of the effective left ventricular filling pressure provided, of course, that neurohumoral influences have not induced a skip from the function curve on which the ventricle was originally operating. In fact, my colleagues and I have spent the last five years in underscoring and attempting to interpret the significance of precisely this type of relationship [11 15] Such an increase in filling pressure is obviously also felt by the pulmonary vascular bed with which the left ventricle is in direct continuity during diastole and is therefore pertinent to our subject The plot between the ventricle's filling pressure and its stroke work is termed a modified Starling or ventricular function curve as seen in figure 1, a figure I show here with the kind permission of Dr Marion Cotten from whose article with Stopp [16] it has been reproduced It was purposely selected for presentation before this group because, in addition to showing the general shape of the left ventricular function curve, it also contains information our own work did not include, namely, the increased work that will be done from any given filling pressure under the influence of the glycosides, in this instance, ouabain If, as was apparently the case from scrutinizing the data

* Used here in the physiological and not in the strictly physical sense

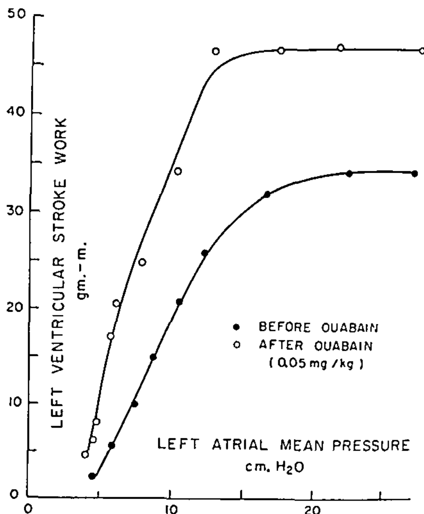



FIG 1 —Ventricular function curves obtained before and after 0 05 mg /Kg of ouabain showing the increased contractility of the ventricular muscle produced by the drug The absence of heart failure is apparent from the high stroke work values obtained before administration of ouabain in a 13 7 Kg dog (After Cotten, M deV and Stopp, P. E Am J Physiol *192* 114, 1958)

of these authors, the glycoside treated heart was initially free of any of the stigmata of failure, I believe these data deserve widespread attention since they may constitute a significant step in resolving the dilemma surrounding the problem of glycoside action on the nonfailing heart However, to return to the theme, my colleagues and I subscribe to the belief that the experimental demonstration of a family or related series of such ventricular function curves may extend by a certain amount the leverage one can apply to the understanding of various circulatory phenomena In this instance, it may be helpful to re-emphasize the fact that the failing ventricle exhibits a performance which is most readily characterized by the experimental observations showing (1) that its function curve is shifted to the right, especially in the upper

ascending and transition portion of the curve, (2) that its peak or plateau is depressed, and (3) that it may exhibit a descending limb. The induction (by means of preferential compromise of the left coronary artery) of *unilateral* left ventricular failure [12] leaves little doubt that such phenomena can occur. Now, if the left ventricle is to maintain a normal or even subnormal stroke volume and produce a normal or near normal aortic pressure and, if because of the presence of failure its function curve is shifted as described above, it follows that the required hydrostatic filling pressure will either approach or exceed the blood's oncotic pressure depending upon the extent to which failure has supervened and its function curve has been shifted. The implications for pulmonary capillary pressure changes and therefore for the subject at hand appear self evident.

The immediately previous paragraphs dealt with the function of the left ventricle which, for our present purposes, might more properly be termed the muscular pump which provides for the egress of blood from the lungs. It is necessary to pause only long enough in the right ventricle to acknowledge that it is the muscular pump which provides for the inflow of blood into the lungs and to remark that the same considerations which relate to the performance characteristics of the left ventricle also apply to it. Passing in a retrograde manner back through the right ventricle to the veins, we are then in a position to close the circle. For in the last instance, the right ventricle, as the left, is a rhythmically contracting but unknowing bit of muscle which, if normal or relatively so, cheerfully passes along that blood which comes to it. It varies, under neurohumoral and biochemical influences, only in the filling pressure which it requires to do any given job. How much comes to it from the veins will depend not only upon the rate of entry of blood into the veins, but also, and to an important extent upon how much the veins are "willing" to contain at any given pressure, that is to say, the state of their tone or physiologic distensibility.

The closing of the circle, frequently desirable when studying the circulation, now requires the reintroduction of one additional bit of prior information.[7] This is shown in figure 2. It demonstrates that when a complete interruption of aortic flow with a clamp was done for a period of 30 seconds, aortic root pressure rose and left atrial pressure rose 46 mm Hg (fig. 2A). Pressure in the carotid sinuses distal to the occlusion was, of course, low. After the inhibition of reflex sympathetic activity by means of ganglionic blockade with Arfonad, the same intervention resulted in an elevation of left atrial pressure of only 7 mm Hg (fig. 2B). Since the resistance to left ventricular ejection was imposed by the clamp in both instances it seems reasonable to attribute the altered response of left atrial pressure after ganglionic blockade to something other than a change in the resistance to left ventricular ejection. Again, by inferential exclusion, sympathetic influence on venous tone appeared to be important. Figures 2B, C and D show the stepwise recovery of the initial left atrial pressure response as the ganglionic blockade wore off.

The idea for a technique which has given rise to the possibility of attacking the problem of recording venous tone simply enough to associate this measurement with other multiple measurements apparently first arose in the minds

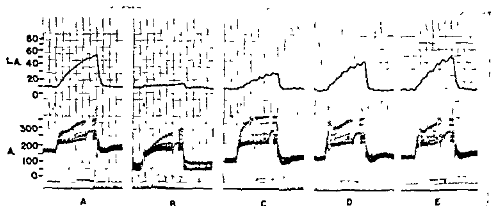



FIG. 2.—Pressure tracings (mm Hg) from left atrium (L.A.) and root of aorta (A) in the dog. Vagus nerves cut. Aortic root occlusion at the beginning of each signal and release at the end. A, B, C, D, and E are six minutes apart. Two minutes after each aortic occlusion, 0.5 per cent of dog's weight of isotonic saline was given. Arfonad (Ro 2-2222), 0.05 mg. per kilogram, given intravenously two minutes prior to B. Time signal = 1 second. (After Sarnoff, S. J. and Sarnoff, L. C.; Circulation 6: 51, 1952.)

of Drs. Connolly and Wood[17] of the Mayo Clinic. They constructed a balloon small enough to be inserted into a peripheral vein in the hope that a change in the force of the vein's contraction would reveal itself as a change in the balloon's intraluminal pressure. Their efforts were, as I understand it, unhappily not completely successful. However, Salzman and Leverett[18,19] then developed a thicker-walled and much less distensible micro-balloon with which they did appear to obtain encouraging results. The latter investigators generously made some of these balloons available to our laboratory.

With our use of this technique the balloon is introduced into a peripheral leg vein in the dog through a distal venotomy and distended with water under that head of pressure which will just appose it to the vein wall. Proper position and filling is signaled by the appropriate response of its intraluminal pressure with a sympathetic stimulus such as bilateral common carotid artery occlusion. Local venous pressure, that is, the pressure in the vein at a point just cardiad to the balloon, is also recorded. Figure 3 shows the responses to bilateral common carotid artery occlusion in such a preparation. The change in the venous balloon pressure paralleling the rise of arterial pressure with little change in local venous pressure has as its most plausible explanation, as indicated by Salzman[19] that an increase in venous as well as arteriolar tone occurred during the period of carotid sinus hypotension. Attention is drawn to the overshoot or downward rebound after release of the carotid arteries since this phenomenon will appear in the next slides. Figure 4, recorded at a somewhat higher speed, shows the previously described experiment of total aortic occlusion but with venous tone recording added. Prior to ganglionic blockade (at the left) the marked elevation of left atrial pressure during aortic occlusion was accompanied by evidence of increased venous tone, that is, decreased venous distensibility. After ganglionic blockade, when venoconstriction was not apparent during the aortic occlusion, the elevation of left

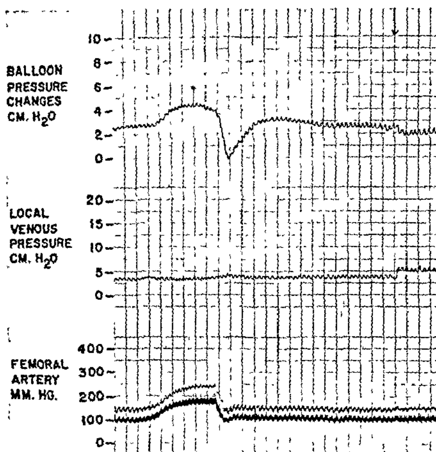



FIG 3.—Changes in pressure in venous microballoon (top) local venous pressure (middle, see text) and femoral artery induced by bilateral common carotid artery occlusion during 30-second period shown by signal at the bottom. 30 ml. of Dextran infused at the arrow. Time is 10 seconds per large box.

(Figure 3 published by permission from Sarnoff et al. Graded reduction of arterial pressure in man by means of a thiophanium derivative (Ro 2-2222). Circulation 6: 63, 1952.)

atrial pressure was substantially diminished. Similar results were obtained with the adrenergic blocking agent, dibenzyline. Some pundit has defined wisdom as that opinion which reflects one's own previous views. I sometimes feel the same way about biophysical instrumentation. In this instance, the results obtained with the micro-balloon so closely coincide with my own prior prejudices that I am very nearly induced to believe that the information recorded with it is valid. In a more serious vein, however, it would be a disservice to you to omit remarking that certain precautions must be taken in the use of this promising tool and that all the required precautions are not, as yet, clearly understood.

Such reservations notwithstanding, I nevertheless believe that such data introduces the possibility of extending the interpretation of previously ob-

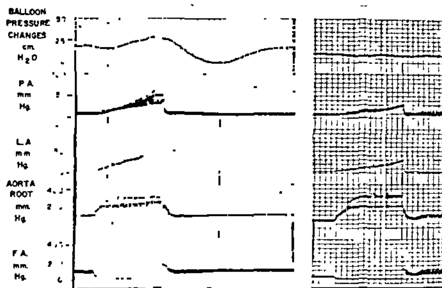



FIG. 4.—*Left* Changes in pressure in venous microballoon, pulmonary artery (P.A.), left atrium (L.A.), root of aorta and femoral artery (F.A.) during period of aortic root occlusion shown by signal at the bottom *Right* Same but after ganglionic blockade with 0.04 mg./Kg. of Arfonad (Ro 2-2222) intravenously. Time signal = 1 second

(Bottom half of Figure 4 published by permission from Sarnoff, S. J. and Sarnoff, L. C. Neurohemodynamics of pulmonary edema. II. The role of sympathetic pathways in the elevation of pulmonary and systemic vascular pressures following the intracisternal injection of fibrin Circulation 6: 51, 1952.)

served phenomena one step beyond the stage of inferential exclusion. It would appear that, when sympathetic stimulation induces systemic vasoconstriction, it is well to consider not only the influence of the increased resistance to ejection from the left ventricle and the performance characteristics of the left ventricle at that time, but also the extent to which a decrease in venous distensibility induces a brief period of disequilibrium during which the change in the venous blood volume is reflected, via the right heart, in an augmented pulmonary blood volume and pressure. It is difficult to imagine an experiment in which it is possible to modify tangibly any single parameter of the circulation without also inducing myriad reflected changes in its other parameters. It will, therefore, be simple for me to persuade you that the above exposed view must be lacking to a considerable extent in not having included an appreciation of those factors which we have not, as yet, had the wit to examine.

The above treatment of the subject at hand was predicated on the experimentally supported hypothesis that, in a normal vascular bed edema will supervene when the oncotic pressure of the blood is, for an appreciable interval, exceeded by the hydrostatic pressure in the capillary by an amount which promotes the formation of tissue fluid at a rate not readily handled by the lymphatic run-off. I would not have complied with the express wishes of our chairman if I did not at least touch on that highly interesting but little

understood clinical phenomenon wherein overt manifestations of lung edema are not observable even though left atrial pressures are markedly elevated. The question thus naturally arises as to whether there is some alteration in the pulmonary capillary-alveolar barrier. Although it was perhaps overly obdurate on my part, I nevertheless retained some rather pale reservations in this matter since no information had come to my attention about the recording of such elevated left atrial pressures for more than very brief periods of time. This aspect of the matter was clarified, however, by Dr. Samuel M. Fox III and Dr. Andrew G. Morrow in the National Heart Institute's Clinic of Surgery. They observed, by means of Dr. Morrow's technique of transbronchial catheterization, recorded left atrial pressures twice the normal oncotic pressure of the blood and continuously observed these for more than half an hour on three separate occasions without observing the overt manifestations of lung edema. You may recall, Mr. Chairman, that earlier in this symposium I addressed a question about the appearance of the lymphatics in such lungs to the eminent members of the pathology panel. It would appear that this is not one of our most precisely defined areas of knowledge. Eventual conviction in this matter will, I suppose, await evidence of the type obtained by Drs. Fox and Morrow together with evidence in the same patient concerning the presence or absence of an abnormally capacious lymphatic system. My own uninformed guess is that there may be some increase in the resistance of fluid transfer from capillary to alveolus in the lungs of patients subjected to long-standing pulmonary vascular hypertension and this position is consonant with Dr. Dexter's interesting observations that such patients appear to go into and emerge from lung edema in a more leisurely manner than is usually observed. Anyone interested, however, should acquaint himself with the views of Dr. Graham W. Hayward[20] with whose position such observations are equally consonant.

I close with the feeling that I have not really spoken of anything that most of you did not already know to a varying extent and with varying degrees of conviction. I have the hope, however, that some of you may acquire some pleasure in looking at the syndrome of lung edema from the point of view, necessarily incomplete, that I have attempted to present, namely, a consideration of the net effects of those influences which resist the diminution of pulmonary blood volume via the left ventricle *vis-à-vis* those influences which tend to augment it via the right ventricle. I have, for obvious reasons, omitted any mention of changes in pulmonary venular or venous distensibility although changes thereof would certainly be of considerable interest from several points of view if experimental evidence on this point were available.

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## DISCUSSION

KATZ Coming back to pulmonary edema, I think Dr Sarnoff has added one element which may raise the pressure in the pulmonary circuit It has been generally accepted that left heart failure, operating "backwards," can raise the pulmonary vascular pressure, and hydrostatically, therefore, lead to edema Dr Sarnoff has experiments, which others have also considered, in which systemic veins contract and lead to a redistribution of blood between the systemic and pulmonary circuits in which the pulmonary circuit is distended, its pressure raised, and so hydrostatically might lead to edema

We have been interested in the clinical problem that small pulmonary emboli can give rise to pulmonary edema and death Unless one accepts Wessler's observation, that what the pathologist finds is just the residue of more extensive embolization after agonal lysis has occurred which caused some

of the clots to disappear, one must alternatively consider the possibility of some potentiating mechanisms

Our own work on these potentiating mechanisms has been published in the December issue of the American Journal of Physiology and the January issue of Circulation Research This is a summary of my group's extensive four year study on starch emboli and the mechanisms involved in leading to pulmonary hypertension and bilateral pulmonary edema

Among our findings we concluded that we had evidence that there was pulmonary venoconstriction following embolization as evidenced by a rise in pulmonary arterial wedge pressure (and venous pressure) without an accompanying rise in left atrial pressure That such wedge pressure rises occur was substantiated by Visscher and his group with endotoxin and was shown earlier by Carl Schmidt and Aviado

We were able to demonstrate that unilaterally injected starch (and we proved this by microscopic sections of the lungs and by triturating the several lung lobes and getting the starch content) caused bilateral pulmonary edema This was not caused by airway passage, because we could obstruct the bronchus of one lung and still get it there

Our evidence suggests that it is due to a local pulmonary infarction (It could be produced by local infarction with NaOH ) It operates by liberating humoral substances, nature unknown, and/or by neurogenic reflexes—potentiating mechanisms operating at a distance We could abolish the edema formation to a certain extent by sympatholytic agents We could abolish it by antihistamines We have found that serotonin causes pulmonary edema in the absence of left heart failure

In the experiments I am talking about, the left atrial pressure did not rise In some experiments the pulmonary venous pressure did rise even though the left atrial did not, and in all of our experiments the pulmonary arterial wedge pressure rose However the level reached in the pulmonary veins and arteries was not such that hydrostatic-oncotic pressure differences could explain the edema formation

Therefore we have been forced to the conclusion that in these peculiar circumstances starch emboli operate at a distance by way of a neuro-humoral mechanism to affect the permeability of the capillary wall This is an interpretation by exclusion In some recent, and as yet unreported data small quantities of serotonin injected into the lung circuit were found to produce the same kind of changes including pulmonary edema

If one is permitted to draw deductions by extrapolation, we think that it is possible serotonin might be one of the substances liberated, as shown by Comroe and might have an effect not only in causing the pulmonary hypertension but also in increasing the capillary wall permeability

SARNOFF I should like to indicate the seriousness with which I regard the importance of the pulmonary venous bed and the potential addition to our knowledge about it that may, possibly, be made by Dr Katz' group It has been an area which I have found extremely difficult to attack with methods that carry any conviction It is clear that a change in pressure-volume relationship of the pulmonary venous bed can be a matter of considerable impor-

tance, not only in relation to pulmonary edema but to cardiac output as well There is no definitive information of which I am aware that is available on the subject

I think that the evidence that Dr Katz recited is interesting but there is one point about which I must inquire I believe I heard Dr. Katz say that there was an elevation of the pulmonary venous pressure in the absence of an elevated left atrial pressure If this is true then one would expect to find some evidence of a pulmonary venous sphincter at the junction of these vessels and the left atrium

KATZ. May I suggest that we do what was suggested many years ago in the Royal Society of Great Britain, namely, that when people are in disagreement they get together and do the experiment together and publish what they find jointly

CHAIRMAN WOOD I have one simple question

In the wedge pressure tracing which you have taken during the period of venous constriction, is the tracing an undamped left atrial pressure or is it a sort of mean pressure tracing?

KATZ In connection with these curves I think it should be pointed out that there are some people who do not believe that you can get a true wedge pressure in the dog These wedge curves are not damped arterial pressure curves, but they are damped venous curves They are not undamped left atrial pressure curves I don't know why this is so

I might say that in the hepatic vein there is a sphincter present in certain species but not in others, nor in man

Finally, I wish to restate that in the starch emboli experiments in the dog we found elevation in pulmonary venous pressure, of the order seen in the wedge position, unaccompanied by any rise in left atrial pressure

FORSTER The classical idea of the mechanism of formation of pulmonary edema that I remember from medical school is just what Dr Sarnoff has mentioned—that there would be a movement of fluid into the alveolar septa and from thence into the alveoli I also believe it is a more or less general idea that this will cause edema of the septa before producing fluid in the alveoli This should be an ideal process to follow with measurements of the pulmonary diffusing capacity We would expect a decreased diffusing capacity in the alveoli affected because of the increased diffusion path

The relatively small number of experiments reported, mostly those of Dr M H Williams, Jr (Am J Physiol *175*. 84, 1953) on pulmonary edema in dogs, suggest that what actually happens is that some alveoli are completely flooded with fluid and the remainder are relatively normal In other words this is apparently a patchy mechanism I thought that this would be a good opportunity to ask Dr. Sarnoff for his comments as to whether histological sections were done as a part of his studies and, secondly, to ask the pathologists as to whether they see edema of the septa in pulmonary edema We would like to reconcile our physiological findings with the pathological studies

SARNOFF I have only one word with regard to that—"sorry." We have no information on that

# Pulmonary Vascular Resistance in Mitral Valvular Disease

*By* Kenneth W. Donald

During the last two days our limited knowledge of the pulmonary circulation has been so well ventilated, that we may be in danger of intellectual acarbia and even spasmophilia. It is my task to review the problem of pulmonary vascular resistance in mitral valve disease. It is hardly necessary for me to emphasize the importance of the occurrence of increased pulmonary vascular resistance in mitral stenosis. Mitral stenosis itself can only cause a two to three fold increase in the pressure against which the right ventricle must work. However, if the pulmonary vascular resistance increases, this pressure becomes very much greater and has a major influence on the progress and prognosis of the patient. I must make it quite clear that I have brought no important message or new discovery about the apparently fortuitous occurrence of increased pulmonary vascular resistance in mitral stenosis. Having declared my ignorance, I wish to underline it by briefly reviewing present knowledge, our own experience and some of the theories that have been advanced.

First, there is little need for me to stress the relative crudity of the accepted methods of calculating the pulmonary vascular resistance by relating the mean pressure gradient across the lungs to the mean blood flow. Dr. Cournand has already emphasized the great difficulty in obtaining reliable pressure gradient measurements with the extreme variations of pulse and intrapleural pressures encountered in heart disease. If flow ceases at any time during diastole or if there is critical opening and closing of the smaller vessels in the lungs, then the errors will be even greater. Standstill and even retrograde flow appears to occur in the larger systemic arteries of some animals but DuBois' studies of the pulmonary capillary blood flow, using the body plethysmograph and nitrous oxide absorption would suggest that blood flow does not cease in the pulmonary circulation. There is also inertia and compliance involved in the present method of assessment of pulmonary vascular resistance. Yet increased pulmonary vascular resistance is a very real thing which threatens the life of many patients with mitral stenosis. There is a story from the First World War concerning the remark of one soldier to another who was complaining of the 5 feet of water in the shell hole in which they had taken cover. "If you know a better hole, go to it." I will therefore use the traditionally calculated pulmonary vascular resistance, aware of its many faults but still believing it is a very useful measurement. The units of dynes second $cm^{-5}$ are very impressive ones and are inclined to make one feel one is two steps ahead of Einstein. However, they are the correct units and I will make no further apology for using them.

The problem of the out-flow pressures of the lung circulation has largely

resolved itself through the use of wedge pressures Despite early criticisms of the interpretation of these pressures, more and more studies have shown a remarkable concordance between left atrial pressures obtained by direct puncture and wedge pressures, particularly when these are abnormally raised There is little doubt that, if proper precautions are taken, the impacted segment *of lung vasculature acts as a very effective extension of the catheter* to the pulmonary veins and atrium. This is very useful for measuring mean pressures but has too many undesirable and unpredictable characteristics for the transmission of detailed wave forms. I would like to pay tribute to Doctors Werko and Dexter who are present today, for their work in this field.

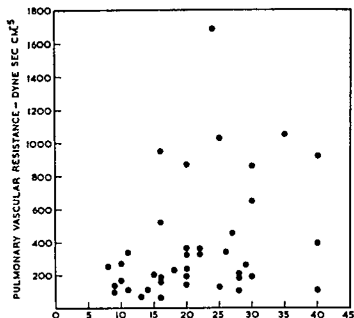
In the last few years a number of textbooks and workers have stated quite categorically that the increase in pulmonary vascular resistance is caused by a *reflex* initiated *by the* raised *left* atrial and pulmonary venous and capillary pressures Some go even further and state that the critical level of left atrial pressure which precipitates this reflex vasoconstriction is of the order of 25 mm Hg This slide (fig 1) shows the pulmonary vascular resistance plotted against the wedge pressure in 44 casually selected patients with mitral stenosis and it is clear that this claimed relationship is not a true one, although markedly increased pulmonary vascular resistance is not found unless there is an abnormally raised left atrial pressure There are, however, many patients with greatly increased wedge pressures who do not show any increase in pulmonary vascular resistance

I have not so far discussed mitral regurgitation Dr Paul Wood, our Chairman, pointed out some years ago that the pulmonary vascular resistance in mitral regurgitation is rarely of the order encountered in many cases of mitral stenosis This state of affairs could be well described as *benign systolic* left atrial hypertension

Helen Duke and other workers have shown in dog experiments that if the left atrial pressure is gradually raised artificially, the pulmonary vascular resistance falls and is minimum at an out-flow pressure of about 15 mm Hg With higher out flow pressures the pulmonary vascular resistance remains at this level The most obvious explanation of this finding is that the pulmonary vascular bed is passively distended and thus resistance is decreased Above 15 mm Hg the pressure volume relationships are such that little further distention occurs Recently we have found in patients with essential systemic arterial hypertension, and normal wedge pressures at rest, that if the wedge pressure rises moderately on exercise, there is a slight but definite fall in pulmonary vascular resistance

At present there is no firm foundation for the claim that pulmonary vasoconstriction is precipitated by an increase in left atrial pressure It is possible that pulmonary vascular resistance is increased by reflex stimulation from the hyperventilation of the lungs It is also possible that a low blood flow throughout the body causes an increased arteriovenous oxygen content difference and increased mean oxygen tension in the chemoreceptors in the systemic circulation Daly and other workers have some recent evidence that this may be of some importance in relation to the pulmonary vascular resistance

However, there is increasing evidence of some autonomic control of the



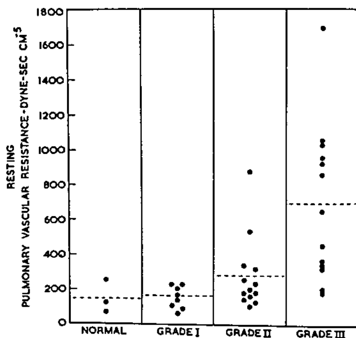




FIG 1 —(*top*) Pulmonary vascular resistance related to mean pulmonary wedge pressure in 44 patients with mitral stenosis

FIG 2 —(*bottom*) Resting pulmonary vascular resistance in patients with mitral stenosis grouped according to the degree of cardiac output response to exercise (See also figure 3)

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has demonstrated that the increase in pulmonary vascular resistance is largely reversible even in patients with severe pulmonary hypertension and with gross pulmonary arterial pathology.

Before proceeding further, let us review some of the relationships found in mitral stenosis. It is well known that patients who have a normal pulmonary vascular resistance and only slightly raised pulmonary arterial pressures are rather more prone to attacks of pulmonary edema than those patients, usually the older ones, who have a high pulmonary arterial pressure and pulmonary vascular resistance For this reason it has been postulated that pulmonary vasoconstriction "protects" *the pulmonary capillaries from sudden rises* in pressure on exercise and thus the risk of pulmonary edema is lessened The true pulmonary capillary pressure is, of course, mainly dictated by the pressure in the left atrium and pulmonary veins and it is difficult to see how pulmonary vasoconstriction can influence it. It merely raises the pressure behind the pulmonary arterioles We do not see peripheral edema in patients with severe systemic hypertension and healthy hearts

There is no doubt that if the pulmonary vascular resistance is raised the right ventricle becomes increasingly overloaded and that right ventricular insufficiency supervenes earlier I do not necessarily mean the state of failure described in clinical practice when there is a rise of right ventricular filling and venous pressure at rest, but rather an increased filling pressure and impairment of cardiac output which may only occur on exercise

The next slide (fig 2) shows the pulmonary vascular resistance at rest related to the degree of response of cardiac output to exercise, and it will be seen that those patients with high pulmonary vascular resistance show an increasing impairment of cardiac output response The various grades of impairment of cardiac output response to exercise are those usually employed by our laboratory and are illustrated in figure 3 It has been considered likely that such patients with impaired exercising cardiac outputs will have less surge behind the mitral valve on exertion, and thus the danger of acute pulmonary edema will be decreased Yet such patients usually show very high wedge pressures on exercise and I feel it is more likely that these patients are less prone to pulmonary edema because of *their ventilatory distress and feelings of weakness associated with low cardiac outputs Thus the periods of dangerously* raised pulmonary capillary pressures are shorter and the risk of pulmonary edema is proportionately less It is certainly wrong to call this increase of pulmonary vascular resistance resulting in right ventricular insufficiency "protection" insofar as, although a further hemodynamic deterioration may lessen stress on the abnormal system, it is not an adaptation in the biological sense but merely one fortunate turn of events amidst many unfortunate ones. *A patient with mitral stenosis who develops paralysis of his legs is equally* protected by his added abnormality

There is also a reasonable correlation between these values at rest Although there is a tendency to a decreased resting cardiac output with high wedge pressures, this is by no means invariable and some patients with a high wedge pressure maintain a normal cardiac output. There is a better correlation between the resting cardiac output and the pulmonary arterial pressure It is still

pulmonary vascular resistance and it may be well worth while to strip the autonomic nerve supply from the hila of the lungs during mitral valvotomy. This would be at present a very empirical procedure but it is possible that such a removal of the autonomic nerve supply may prevent pulmonary vasoconstriction after the operation or during subsequent re-stenosis

The next aspect of this problem is that of the morphological changes that occur in the pulmonary arteries. It has been demonstrated during this symposium that there are many considerable changes in the pulmonary arteries in mitral stenosis There is still debate as to whether there is a true hypertrophy of the media of the pulmonary arteries I will leave this argument to the pathologists who have already had their say Last night I dreamt a thousand diseased arteries danced before me There is however one finding in mitral stenosis that impresses me and that is the appearance of muscle in the walls of the pulmonary arterioles or precapillaries where it does not normally occur

Earlier reports relating vascular pressure to morphological changes in the pulmonary arteries found in lung biopsy emphasized that, although the changes were more marked with higher pressures, this was not consistent Again it was stated that marked changes in the pulmonary arteries rendered a good result with considerable fall in pulmonary vascular resistance less likely, although it was admitted that there were exceptions to this Heath and Whitaker found a much closer correlation between the pressures and arterial changes in mitral stenosis All patients with pulmonary arterial pressures above 70 mm Hg showed marked pathological changes in the muscular arteries and a medial development in the arterioles Below 50 mm Hg no such changes were found

This is an important finding as it would indicate that neither marked pathological changes nor medial "hypertrophy" occur at levels of pressure due to mitral obstruction alone, and that the increase of pulmonary vascular resistance occurs in normal pulmonary arteries The hypertrophy of the media, if it occurs, is secondary therefore to the pulmonary hypertension and does not initiate it

There is little doubt that the degree of vasometricity is increased in patients with mitral stenosis and pulmonary hypertension, as can be demonstrated by the considerable rise of pulmonary vascular resistance on exercise and the considerable fall during sleep and with the administration of acetylcholine Scott and his colleagues showed a significant fall in pulmonary vascular resistance in patients with mitral stenosis and raised pulmonary vascular resistance when tetra-ethyl ammonium chloride was administered whereas Fowler had previously demonstrated that subjects with normal pulmonary vascular resistance showed but little change The effect of anoxia would be of great interest but the few workers who have explored this avenue report that the procedure is too dangerous in such subjects to justify a series of experiments

It would appear reasonable to suppose that the increasing arterial degeneration and intimal thickening, encountered in this disease, will render the increase in resistance largely irreversible. However, just as the hypotensive agents in systemic hypertension have shown this morphological explanation of sustained hypertension to be inaccurate, so the effect of mitral valvotomy

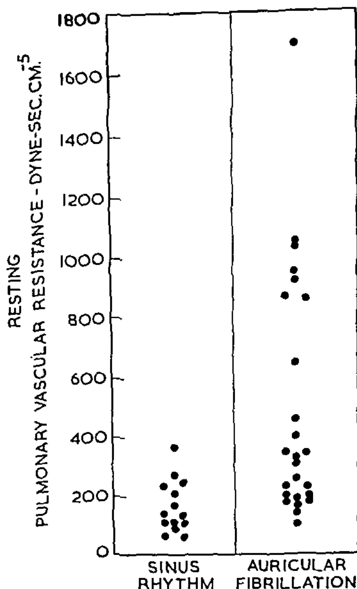



Fig 4 —Pulmonary vascular resistance in mitral stenosis in patients with sinus rhythm and auricular fibrillation

The next slide (fig 5) relates the pulmonary vascular resistance to age It is difficult to be sure of the period of the disease process but it is reasonable to assume that the damage commenced in childhood in most cases There appears to be on the whole an increased incidence of high pulmonary vascular resistance as age increases although a number of younger people do show high values The somewhat lower levels of pulmonary vascular resistance in the last two age groups from 55 to 65 is of interest as the low resistance may be the

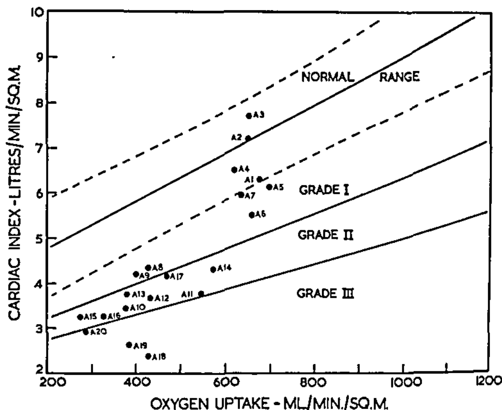



FIG 3 —Cardiac output related to oxygen uptake during exercise. The normal regression line and the 95% confidence limits are shown Three arbitrary grades of impairment of cardiac output response are delineated

very mysterious how the cardiac output falls to abnormally low levels in these patients before there is any clinical evidence of right ventricular insufficiency and failure If the cardiac output remained normal in many of these patients with increasing mitral valve obstruction, then fatal pulmonary edema would appear almost inevitable It is easy to describe the benefits of this reduction of flow but the mechanism is not yet understood The reduction in resting and exercising cardiac output may be due to the development of auricular fibrillation but it also occurs in some instances where there is sinus rhythm

The next slide (fig 4) shows the pulmonary vascular resistance in relation to rhythm and demonstrates that none of the patients in sinus rhythm have a marked increase of pulmonary vascular resistance It is possible that an increased pulmonary vascular resistance and auricular fibrillation are both phenomena commonly occurring in the later stages of the disease It is also possible that auricular fibrillation is partly precipitated by right ventricular insufficiency and a raised filling and atrial pressure although of course the rheumatic changes in the atrial wall must be another important factor However the absence of a raised pulmonary vascular resistance in the presence of sinus rhythm is worthy of further investigation

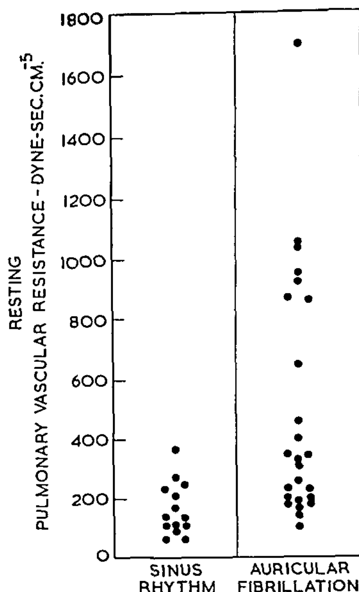



FIG 4.—Pulmonary vascular resistance in mitral stenosis in patients with sinus rhythm and auricular fibrillation

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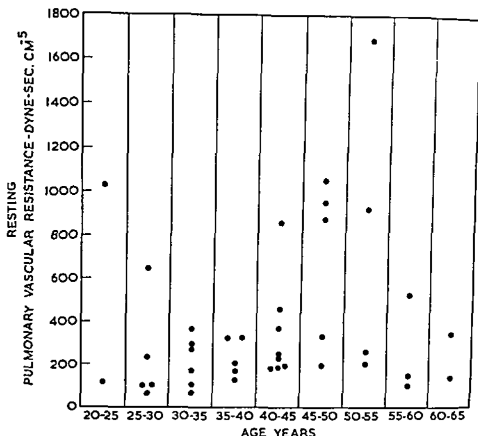



FIG 5—The pulmonary vascular resistance in mitral stenosis plotted in 5 year age groups from 20 to 65 years

reason for their survival to this age An even larger series would be necessary to be at all certain of the significance of these relationships

There is another hypothesis concerning the pulmonary vascular resistance which I would like to present for your consideration As is well known the compliance of the lung is usually considerably reduced in mitral valve disease *It is possible that hemodynamic differences particularly of the venous and* arterial pressures in different parts of the lungs may cause considerable differences in compliance in these regions If the patient is upright, as both fit and unfit cardiac patients usually are, one would expect the bases of the lungs to be less compliant This may cause the tidal air to pass largely into the more compliant lung and the less compliant lung to be underventilated Such underventilation would cause a drop in alveolar oxygen tension in these areas with *possible vasoconstriction This theory that the cardiac patient only uses a part* of his lungs, would explain many findings It would explain the increased ventilation in many cases with a low $pCO_2$, a relatively normal $pO_2$ and high pH It would explain the poor distribution of inspired air demonstrated in mitral stenosis It would explain the relatively normal pulmonary blood volume as measured by dye techniques, *and the fall in pulmonary arterial* pressure when oxygen is given to these patients Careful studies of the pulmo-

nary vascular resistance when breathing raised tensions of oxygen are yet to be carried out and will be of great interest

There are other findings which may also support this possibility. Both radiological and pathological studies of the arterial and congestive changes in the lungs in mitral stenosis have emphasized that the abnormalities are far more marked in the lower lobes Further, Scott, when he demonstrated the acute fall in pulmonary vascular resistance with tetra-ethyl ammonium chloride in this disease, also noticed a very definite fall in arterial blood saturation and it is tempting to think that he had allowed blood to flow through non-compliant, poorly ventilated areas of lungs where the oxygen tensions were low and there was vasoconstriction Dr Soderholm has some other work to report later this morning which might appear relevant to this aspect

It is also possible that the greatly increased negative intrapleural pressures in this disease owing to decreased compliance and increased ventilatory volums, may cause some degree of capillary collapse and increased pulmonary vascular resistance It is obvious that the excellent work that Riley and his colleagues reported yesterday may have important repercussions in the lung circulation in mitral stenosis

Finally, one cannot discuss pulmonary vascular resistance in mitral stenosis without considering the effects of mitral valvotomy I will however delay discussion of our findings until Dr William Likoff has presented his results

In conclusion I would like to re-emphasize that we still do not know why increased pulmonary vascular resistance occurs in many patients with mitral stenosis It is certainly associated with a raised left atrial pressure and is largely relieved by a fall of this pressure after mitral valvotomy. The personal variation in this response to the abnormal hemodynamic situation is as mysterious as the onset of essential hypertension Despite the great success of mitral valvotomy in a certain number of cases there is still great need for some therapeutic agent that will prevent pulmonary vasoconstriction in this disease Although a high pulmonary vascular resistance, by causing right ventricular embarrassment, may play a part in preventing acute pulmonary edema, it is most probable that its development considerably shortens life in the large majority of cases

(I wish to thank Drs J M Bishop and M Bateman for their help in preparing the data shown )

# The Vasoconstrictive Factor in Pulmonary Hypertension

*By* Paul Wood

In a study of 500 cases of critical mitral stenosis (orifice 5 x 3 mm to 1.5 x .75 cm ; usually 1 x .5 cm ) the pulmonary vascular resistance was extreme (over 10 units) in 12 per cent, and moderately high (6 to 10 units) in 16 per cent.

The 60 patients with an extreme resistance were selected for further study. The average age of these cases (39) was the same as that in the cases with relatively normal resistance, and 80 per cent of them gave no history of previous hemoptysis, pulmonary edema, paroxysmal nocturnal dyspnea, orthopnoea or even severe breathlessness, their first important symptoms being those known to be a consequence of severe pulmonary hypertension and a low cardiac output, particularly fatigue, hepatic discomfort and edema. It was concluded that the high resistance developed pari passu with the stenosis, and was not a late consequence of chronic interstitial edema of the lung or the other manifestations of prolonged pulmonary venous congestion. It followed that some active physiological process was at work, presumably reactive pulmonary vasoconstriction. The remarkable fall in resistance that followed technically successful valvotomy seemed to confirm the thesis, although gradual involution of organic vascular disease might also have resulted from the abolition of passive pulmonary hypertension.

To demonstrate the presence or absence of pulmonary vasoconstriction I decided to try acetylcholine in the hope that a suitable dose might prove selective, the rapidity of its destruction by cholinesterase making it likely that it would not reach the systemic circulation. In fact, a dose of 1 mg injected rapidly into the pulmonary artery had precisely the effect we desired: the pulmonary blood pressure fell and the systemic blood pressure rose. The rise in systemic blood pressure was attributed to an increase in cardiac output secondary to the fall in pulmonary vascular resistance, although this was not always easy to demonstrate.

The effect of acetylcholine was then investigated in sixteen cases of mitral stenosis. In eight the resistance was extreme (12 to 26 units), in four it was high (6 to 10 units), and in four only slightly raised (2.5 to 5 units). In the more elaborate trials a double lumen catheter was passed into one pulmonary artery and a single lumen catheter into the other. The distal aperture of the twin lumen catheter was used to measure the pulmonary artery pressure. The proximal aperture was placed just beyond the pulmonary valve and served both for sampling and for the injection of acetylcholine into the main pulmonary artery. The single lumen catheter was wedged distally so that the left atrial pressure could be measured simultaneously. A Riley needle was

inserted into each brachial artery, one for sampling and the other for recording the systemic blood pressure Oxygen consumption was measured by analyzing two minute samples of expired air collected in a Douglas bag, and pressures were recorded by means of a Sanborn electromanometer and four channeled direct writing instrument An initial trial dose of 0.5 mg of freshly prepared acetylcholine was usually given to test the technical arrangements and to ensure that 1 mg would not prove too much An overdose resulted in a fall of systemic blood pressure and was therefore easy to detect If there was no effect the dose was increased first to 1 mg and then to 1.5 mg, each in 4 ml of normal saline. There was usually an all or none response and larger doses were found unnecessary.

The results were fairly uniform; the pulmonary blood pressure fell and the left atrial pressure rose The cardiac output, blood pressure and pulse rate remained much the same The pulmonary vascular resistance fell from an average of 9 to 5 units The effect was most marked in those with the highest resistances On the other hand, the only 2 cases that did not respond at all had extreme resistances It is suspected that such cases may fail to respond to valvotomy

The effect of this extreme resistance on the total situation in mitral stenosis is multifold —

1 It may become irreversible as illustrated in the two cases just mentioned. Obliterative pulmonary vascular disease is presumably responsible
2. It puts a great strain on the right heart and so causes genuine right ventricular failure.
3 This right heart failure prevents much rise of the left atrial pressure on exercise
4. Indeed, the left atrial pressure may be so little raised as a result of the low output, that valvotomy is unable to improve matters, for it can result in no further fall in left atrial pressure and so cannot reduce pulmonary hypertension by abolishing the passive factor. Failure to recognize this has led to at least one useless valvotomy
5 The sluggish circulation in these cases encourages phlebothrombosis in the legs and death from pulmonary embolism is not uncommon Massive thrombosis in a main pulmonary artery may be another fatal complication.
6 On the other side of the ledger is the protection that a high pulmonary vascular resistance gives to the lungs

### *Hyperkinetic and Reactive Pulmonary Hypertension in Cases with Potentially High Pulmonary Blood Flow*

Whatever we call the Eisenmenger group there is no doubt that that is a most convenient term to identify cases of pulmonary hypertension with an extreme pulmonary vascular resistance and reversed or bidirectional shunt at aorto-pulmonary, ventricular or atrial level; that Eisenmenger's case happened to have a ventricular septal defect instead of one of the other nine anomalies it might have had when seen in life was pure chance

Acetylcholine was given to thirteen cases of the Eisenmenger syndrome with resistances ranging between 15 and 32 units The communication between the two circulations was atrial in 6, ventricular in 5 and aorto-pulmonary in 2 The pulmonary blood pressure did not fall primarily in a single instance,

even with a dose of 2 mg. It seemed possible, however, that a fall in pulmonary vascular resistance might simply increase the blood flow to the lungs without significantly altering the pressure. Accordingly we measured the arterial oxygen saturation simultaneously, thinking that it might rise, but in no instance was any such rise observed. Instead, however, in some cases there was a fall. This suggested the possibility of a paradoxical response and shortly afterwards we obtained an actual rise of pulmonary artery pressure in one case, which seemed to confirm the idea. Then came a report from Adams, Lind and Rauramo (Nov., *1957*) that acetylcholine caused pulmonary vasoconstriction in newborn babes This seemed to clinch the matter and, together with our findings, appeared to confirm Edwards' idea that the pulmonary vessels in Eisenmenger's syndrome remained fetal in character

There were two further surprises in store, however First, we found that acetylcholine lowered the arterial oxygen saturation sharply, as well as the *pulmonary artery pressure, in a case of cor pul monale, suggesting that it may* open up physiologically closed vascular pathways through unventilated lung, and that this might occur to a lesser extent in any kind of patient lying quietly on a catheter table, particularly if premedicated with barbiturate A similar drop in arterial oxygen saturation has since been recorded in a case of mitral stenosis with high resistance, the pulmonary artery pressure falling as usual simultaneously It was felt that the fall in the Eisenmenger group might be similarly explained, despite the lack of a demonstrable effect on the pulmonary blood pressure and resistance

I then wrote to Dawes and asked him if he would be kind enough to check the effect of acetylcholine on the fetal pulmonary circulation in animals, and he has since told me that in his first experiment he obtained a drop in pulmonary blood pressure when using a dose equivalent to ours. No doubt he will elaborate on this shortly

*This leaves the point unsettled, but it should be cleared up with further* work The fact remains, however, that acetylcholine fails to lower the pulmonary vascular resistance in established cases of the Eisenmenger syndrome, at any rate in adults and children over 5 years old Whether this is due to obliterative pulmonary vascular disease or to an unusual physiological response remains to be seen.

One can go further in one respect, however If in the Eisenmenger syndrome one of the pulmonary arteries is stenosed, so that the pressure beyond the stricture is appreciably below systemic level, then the response to acetylcholine delivered to that pulmonary artery is normal, the pressure falling sharply This helps to dispose of the idea that the fault in the peripheral pulmonary arteries in Eisenmenger's complex is congenital

*Hyperkinetic Pulmonary Hypertension*

As previously explained, hyperkinetic pulmonary hypertension without the florid reaction of the Eisenmenger group, implies a slight or moderate rise of resistance, or at least failure of the resistance to fall, otherwise little elevation of pressure can occur, even with flows of 30 liters per minute, for the

pulmonary vessels normally dilate in response to increased flow, and maximum dilatation lowers the resistance to about one third of its resting level

Acetylcholine was given to only three cases of hyperkinetic pulmonary hypertension so defined the pulmonary blood pressure fell 5 mm Hg in two of them, but very little, if at all, in the third Some degree of vasoconstriction is evidently present in this group, but it is not pronounced

### Obstructive Pulmonary Hypertension

No opportunity to give acetylcholine to a case of proved subacute thrombo-embolic pulmonary hypertension has yet arisen

### Primary Pulmonary Hypertension

Of the six cases investigated five responded briskly to acetylcholine Indeed the magnitude of the response was not surpassed in any other condition The test at once distinguished these cases from members of the Eisenmenger group Two of those with the greatest falls of pulmonary blood pressure had had the condition for 8 and 4 years respectively, which should have provided ample time for the development of sufficient obliterative vascular disease to abolish the response Children aged 5 to 8 years with Eisenmenger's Complex do not react in this way to acetylcholine This remarkable difference in behavior cannot be ignored, and may well prove of fundamental significance

In primary pulmonary hypertension vasoconstriction could also be relieved by both priscoline and aminophylline

### Pulmonary Hypertension in Cor Pulmonale

Only two cases of cor pulmonale were investigated and when acetylcholine was given to these each responded briskly enough As stated above, the arterial oxygen saturation fell conspicuously, suggesting that the drug opened up vascular pathways through unventilated lung Both cases had fibrotic rather than emphysematous disease

### Summary and Conclusions

The results are summarized in the accompanying table 1 Omitting obstructive pulmonary hypertension, which has not yet been studied in this way, it is clear that an important degree of pulmonary vasoconstriction can be demonstrated in all forms of pulmonary hypertension except the Eisenmenger group Release of this vasoconstriction by acetylcholine lowers the pulmonary blood pressure and pulmonary vascular resistance and increases the cardiac output The systemic blood pressure may rise secondary to the increased output In mitral stenosis the left atrial pressure rises In all forms of pulmonary hypertension, but especially in cor pulmonale, the arterial oxygen saturation tends to fall This may be attributed to the opening of vascular pathways through unventilated lung

The demonstration of a pulmonary vasoconstrictive factor in most forms of serious pulmonary hypertension and its absence in the Eisenmenger group, takes us only one short step towards our goal We still do not know what causes vasoconstriction, nor how important a part it plays in initiating, aggra-

TABLE 1—*Acetylcholine Test*
*Summary of Results*

| Type of Pulmonary Hypertension | Resistance (units) | No of cases | No. in which P.A.P fell | Av. fall in P.A. systolic pressure (mm Hg) |
|---|---|---|---|---|
| (Mitral stenosis) | | | | |
| Chiefly passive | 2 5— 5 | 4 | 4 | 13 |
| Partly reactive | 6 —10 | 4 | 4 | 17 |
| Highly reactive | 12 —26 | 8 | 6 | 27 |
| Hyperkinetic | 2 — 4 | 3 | 2 | 5 |
| Obstructive | | 0 | | |
| (Eisenmenger group) | | | | |
| Obliterative | 15 —32 | | | |
| Atrial shunt | | 6 | 0 | — |
| Ventricular shunt | | 5 | 0 | — |
| Aorto pul shunt | | 2 | 0 | — |
| Partly hyperkinetic | 8 —10 | 1 | 1 | 5 |
| (Cor pulmonale) | | | | |
| Polygenic | 8 —15 | 4 | 3 | 15 |
| (Primary) | | | | |
| ? Vasoconstrictive | 8 —23 | 6 | 5 | 30 |

vating or maintaining pulmonary hypertension In view of the uniformity of the reaction, however, no matter how the pulmonary hypertension is initiated, it is again suggested that vasoconstriction may develop in response to the high pressure itself and so tend to perpetuate and increase it. The absence of vasoconstriction in the Eisenmenger group, at any rate from the age of 5 onwards, may be due to secondary obliterative vascular disease or to some inherent difference in the behavior of the pulmonary blood vessels in these congenital cases

## Discussion

SODERHOLM We have studied 10 cases of mitral stenosis and in order to get a complete view of the hemodynamics the investigation was performed both at rest and during exercise, in a way that insured steady state conditions Acetylcholine was given by continuous infusion in a dose sufficiently small to be destroyed before it reached the general circulation

The findings of Harris and Wood were fully confirmed, but during exercise the effect of acetylcholine was more pronounced, and in our cases the effect was as great when the pulmonary artery pressure was almost normal as when marked pulmonary hypertension was present We made continuous recordings of the pulmonary artery pressure in ten patients being subjected to light work during the first minutes of acetylcholine infusion. A significant decrease in pulmonary artery pressure occurred immediately and persisted for five minutes Another important finding was that the arterial oxygen saturation after

5 minutes of acetylcholine infusion had decreased markedly. Also there was a significant increase in cardiac output and a significant decrease in pulmonary artery pressure indicating a marked decrease in pulmonary vascular resistance The brachial artery pressure was unchanged The arterial oxygen saturation decreased significantly, although the oxygen consumption remained constant and the pulmonary ventilation increased slightly.

This demonstration that acetylcholine gave a rapid and marked decrease of the arterial oxygen saturation both at rest and during exercise, is a new finding of importance for the evaluation of its action on the lungs This change in arterial oxygen saturation must be due to a shift in the ventilation perfusion ratio of the lungs This could be caused by an increasing dead space ventilation or an increase of intrapulmonary shunts; i e, increased blood flow through poorly ventilated areas It is, however, improbable that such a decrease in oxygen saturation as 6 per cent could be caused solely by an increase in dead space ventilation, especially as the total ventilation was only slightly increased In other studies we showed that the dead space ventilation was decreased during actylcholine infusion and thus the most probable action of acetylcholine seems to be an increase in the intrapulmonary shunting of blood The explanation of this action is probably that in certain parts of the lungs an alveolar hypoventilation exists which affects the vascular bed through an hypoxic stimulus causing a functional restriction of it This situation corresponds to the compensated form of nonuniform ventilation blood flow ratios, as described by Comroe and others When acetylcholine is infused in a steady state vasodilation occurs and the nonuniform ventilation blood flow ratio is revealed, and at the same time the pulmonary artery pressure decreases because of the increased area of the vascular bed The changes found will thus be the results of interference with a definitely established physiological mechanism, rather than any influence on a presumed "protective vasoconstriction"[15]

COURNAND I have two questions for Dr Paul Wood

Firstly, if I understood you well, your results with regard to the effects of a single dose of acetylcholine in the pulmonary artery upon the pulmonary artery pressure in cases of pulmonary hypertension due to mitral stenosis, and other causes, differed with those, first reported by Dr Peter Harris from London, in his medical doctor thesis, published in 1955 (Harris, P, A study of the effects of disease on the pressures in the pulmonary artery and right ventricle in man Thesis, University of London, *1955*) Almost all your cases, regardless of the level of hypertension, showed a pressure drop in the pulmonary artery Peter Harris, on the contrary, in his statistical analysis showed that in cases with normal pulmonary artery pressure or in those with considerable degrees of hypertension, there was no decrease in pressures, whereas in cases with moderate degrees of hypertension, the pressures dropped In this group, he attributed the effect of acetylcholine to its reducing action on the tone of the hypertrophied smooth muscles of the small pulmonary vessels In the other group with considerable hypertension, he considered that the vascular walls acted like rigid tubes as a result of irreversible pathologic alterations

Secondly, it is not clear to me how you were able to measure cardiac output

in your studies For this purpose, in these subjects who were in an unsteady state, did you use the pressure pulse contour method of Remington?

WOOD We took control samples beforehand from the pulmonary artery and the brachial artery We took them again at 30 seconds after the injection when the response was maximum, and again at about two minutes Of course we had to take a 2 minute oxygen consumption That was the erroneous part of the measurement. The cardiac output measurements, as I pointed out, were very rough and not too reliable. It was difficult to measure when it was changing so rapidly It is easier when acetylcholine is given by slow infusion

COURNAND: Our experience with acetylcholine is based on the continuous perfusion of the pulmonary artery with an acetylcholine solution at the rate of 0 5 mg. per minute In only few subjects or patients did the cardiac output increase; in most of them there was no change, even in the presence of a marked drop in pulmonary artery pressures.[6]

I would like to comment particularly on some experiments with continuous perfusion of acetylcholine in patients with chronic pulmonary emphysema These studies, actually in progress in my laboratory, are conducted by Drs Harry Fritts, and Charles Chidsey We have studied 18 cases so far, with all types or grades of pathologic, volumetric or physiologic changes, and with varying degrees of pulmonary hypertension The measurements of pulmonary blood flow are made almost simultaneously by the direct Fick and by the dye indicator methods The dye is injected near the right atrium and two simultaneous curves are obtained by drawing samples from the pulmonary artery and from the brachial artery. The object of these studies with the indicator technique is to determine approximately the effective bronchial blood flow by measuring the output differences between the right and left ventricles, [1] furthermore, by comparing the two curves, instant by instant, an attempt is made to determine the distribution curve of the transit times through the lung, according to the statistical method, introduced by Stanley Bradley for the splanchnic circulation [7] The ultimate purpose is to demonstrate whether acetylcholine perfusion is affecting pulmonary arterial pressure, systemic blood oxygen saturation, and the distribution of the blood transit times through the lungs It appears from the work done so far that [1] the pulmonary arterial pressure decrease does not occur in all instances, [2] although the arterial $O_2$ saturation often drops, this is by no means constant It is too early to comment on changes in the distribution of blood transit times These studies were set up as a test of the hypothesis formulated by Liljestrand and Euler, namely, that in poorly ventilated alveoli, the blood flow is reduced as a result of vasoconstriction caused by the low $O_2$ tension We cannot yet make a definite statement about the operation of this "protective" mechanism; it might be invoked in some cases as demonstrated by a drop in pulmonary artery pressure and in arterial $O_2$ saturation, but in other cases with similar or worse degree of disturbances in ventilation/perfusion relationships, it cannot.

DAWES I will be very brief There are only two points I want to make The first is to confirm that, in very few experiments as yet, acetylcholine does cause vasodilatation in the isolated lamb's fetal lungs I stress the isolation. These, as well as many other previous experiments, show that the pulmo-

nary vessels unquestionably have tone, although they are separated from the central nervous system

The second point is to ask you a question about your extremely stimulating observations on the Eisenmenger complex You showed that the pulmonary arterial pressure did not fall when you injected acetylcholine, and you suggested that this was not due to an increased flow through the hole somewhere in the myocardium or great vessels, because there was no change in the systemic arterial oxygen saturation.

Do you know whether the oxygen saturation was a sufficiently sensitive index to be certain that there was no change in the relative volume of blood flow through a shunt?

WOOD. I think so If you put acetylcholine into the descending aorta in a patent ductus with severe pulmonary hypertension, the arterial oxygen saturation in the descending aorta falls very nicely, demonstrating an increase in shunt reversal as the systemic peripheral resistance falls

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# The Change in Pulmonary Vascular Resistance After Relief of Mitral Obstruction

*By* William Likoff

The past decade has witnessed the establishment of surgical techniques to correct certain acquired heart defects particularly, and most pertinent to this discussion, that which impedes the flow of blood across the mitral orifice During this same interval a more precise methodology has been perfected to record cardio-pulmonary hemodynamics The concomitant availability of devices for correction and measurement has quickened the opportunity to redefine our concepts concerning certain cardiac lesions

The present study which records alterations in the calculated pulmonary vascular resistance after surgery for mitral stenosis is an early, incomplete and perhaps inexpert exploitation of that opportunity. It includes references to: (1) The normal values of pertinent cardio-pulmonary dynamics, (2) The pathophysiologic patterns which develop in mitral stenosis and their devolutionary sequence, (3) The definition of "relief of mitral valve obstruction", (4) The manner in which "relief" alters the pathophysiologic patterns particularly the calculated pulmonary vascular resistance, (5) The factors which may regulate these responses, (6) The deterrents to establishing specific conclusions

## Normal Values of the Pertinent Cardio-Pulmonary Dynamics

The hemodynamic data which have been found most useful in appraising the significance of mitral stenosis are illustrated in figure 1A These determinations require simultaneous right and left heart catheterization which can be accomplished without serious morbidity

## The Pathophysiologic Patterns of Mitral Stenosis

It is reasonable to expect that the abnormal physiologic events which arise as a result of mitral stenosis mature in sequence At least the examination of patient material reveals gradations of physiologic deterioration which appear to form the components of a basic devolutionary pattern

The simplest deviation which arises in response to a reduction in the size of the functional mitral orifice is an increase in the left ventricular filling pressure gradient As seen in figure 1B this may even exist though the remaining hemodynamic values are quite normal. In the next succeeding stage of the physiologic derangement this increased pressure gradient is accompanied by

*The catheterization studies for this report were performed at the Brith Sholom Cardio pulmonary Laboratory, Hahnemann Medical College and Hospital, Philadelphia, Pa. The details of these studies were made available through the kindness and cooperation of Harry Goldberg, M.D., Laboratory Director.*

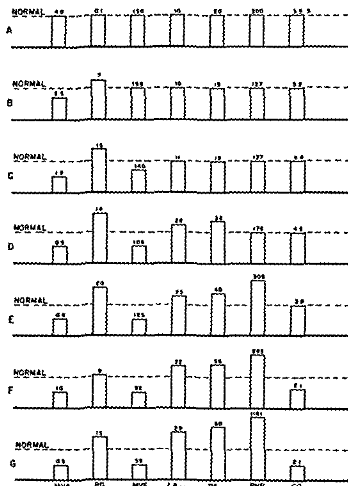



FIG 1 —Normal Values (maximum)

MVA — Mitral valve area (Cm ²)
PG — Ventricular filling pressure gradient (mm Hg)
MVF — Mitral valve flow (ml /V F P /sec )
LA — Left atrial mean pressure (mm Hg)
PA — Pulmonary artery mean pressure (mm Hg)
PVR — Pulmonary vascular resistance (dynes sec cm ⁻⁵)
CO — Cardiac output (l/min )

Progressive stages of pathophysiologic response to mitral obstruction as illustrated by several patients with increasingly severe involvement

A Normal values of pertinent cardio pulmonary dynamics
B An illustration of the earliest pathophysiologic response to mitral obstruction which is characterized by an abnormal left ventricular filling pressure gradient (Patient V K )
C Decreased mitral valve flow in the second stage of the pathophysiologic devolutionary pattern of mitral stenosis (Patient H M )
D. Elevation of left atrial and pulmonary artery mean pressures in the third stage of pathophysiology (Patient M J )
E Only cardiac output remains normal at rest in the fourth stage (Patient C M )
F. Hemodynamic data illustrating the most advanced pathophysiologic pattern (Patient M McG )
G An advanced, if not terminal, pattern marked by a small pressure gradient and a reduced mitral valve flow.

a fall in blood flow across the mitral valve (fig. 1C). The third step is characterized by considerable elevations in the left atrial and the pulmonary arterial pressures (fig 1D) The calculated pulmonary vascular resistance then rises *beyond normal limits (fig 1E). Finally* cardiac output *falls* The exceptional variations from the normal which may be encountered in this last stage are illustrated in figure 1F

This arbitrary classification does not imply that the most advanced abnormalities in hemodynamics are initiated only by extreme mitral valve obstruction Multiple and obscure factors in addition to the extent of the anatomic distortion conspire to motivate the exact pathophysiologic response It has been amply indicated in the prior discussions that this particularly applies to the calculated pulmonary vascular resistance

## Relief of Mitral Valve Obstruction

To avoid compounding confusion it must be stated categorically that mitral commissurotomy and "relief of mitral obstruction" are not necessarily synonymous Hence an inquiry into the changes noted in the calculated pulmonary vascular resistance after surgery cannot be extended to all who have been operated but must be limited to those in whom a standard of accomplishment has been realized

Two different criteria define that standard. The first has been suggested by the surgeons It holds that the valve obstruction has been removed when the orifice permits the passage of two ordinary fingers Since no reference is made to the desired improvement in valve function this definition is more incomplete than unreasonable

*The second definition insists that there is relief of the obstruction* only when the two basic hemodynamic deviations which indicate the presence of the stenosis in the first place are corrected Thus the functional size of the orifice may be considered satisfactorily restored when the left ventricular filling pressure gradient has been reduced significantly and when the mitral valve flow has been returned to normal These criteria are applicable to patients in whom the pressure gradient initially is at least 12 mm Hg

In the more advanced pathophysiologic patterns where disturbances in mitral valve flow are more significant than large pressure gradients (fig 1G) *"relief" is considered accomplished if that flow becomes normal*

It is possible to satisfy both the surgical and physiological criteria (Fig 2A) However in many instances the hemodynamics fail to support the surgeon's claim that the stenosis has been corrected An example of such a result is seen in this patient in figure 2B A low mitral flow persisted in spite of the increased size of the valve orifice Experience such as this suggests that the exacting physiological criteria are a more adequate measure of the relief of obstruction

## The Response to Relief of Obstruction

The ideal response to mitral commissurotomy is seen in Figure 2C The preoperative calculated pulmonary vascular resistance was not elevated

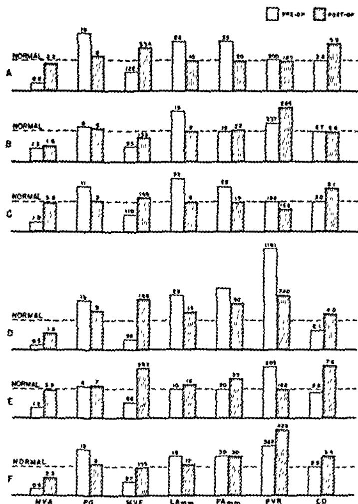



Fig. 2.—(Abbreviations the same as in figure 1) Effect of surgery on physiologic functions in six patients.

A. Physiologic data confirming the fact that mitral obstruction was relieved.

B. Physiologic data indicating a low mitral valve flow and hence the failure to relieve stenosis.

C. An ideal response to mitral commissurotomy.

D. An illustration of the failure to return calculated pulmonary vascular resistance to normal.

E. The return of calculated pulmonary vascular resistance to normal after relief of stenosis.

F. A rise in calculated pulmonary vascular resistance following mitral commissurotomy.

The mitral valve obstruction was considered relieved according to both surgical and physiological standards in the patient illustrated in figure 2D. However although the abnormal calculated pulmonary vascular resistance which existed prior to surgery was reduced it continued to remain elevated.

Figure 2E demonstrates an adequate relief of stenosis in that the valve flow

returned to normal. In this instance the calculated pulmonary vascular resistance also fell to within normal limits.

The last of the preoperative and postoperative comparisons records a rise in the calculated pulmonary vascular resistance even though the left ventricular filling pressure gradient was reduced significantly and the mitral valve flow became normal (fig 2F)

From these results it is clear that calculated pulmonary vascular resistance may be variously influenced when mitral valve obstruction is relieved. If normal prior to surgery it generally remains at that level. However, if elevated it may fall, return to normal or actually rise

## Factors Regulating Response

Theoretically functional influences, organic vascular changes or a combination of both have been held responsible for unusual pressure gradients across the pulmonary circulation In those patients in whom the calculated pulmonary vascular resistance falls to within normal limits following commissurotomy it is consistent with current views to attribute the response to a subsidence of the functional element Conversely when the resistance falls but continues to remain significantly elevated it is a reasonable contention that organic vascular changes account for the continuing abnormality Finally, the explanation for a rise in calculated pulmonary vascular resistance may be predicated upon the thought that the functional element is aggravated by the increase in pulmonary blood flow which develops after the relief of the mitral valve obstruction

## Deterrents to Specific Conclusions

The catheterization studies included in this report were performed 4 to 16 weeks after surgery The full hemodynamic benefits from mitral commissurotomy generally are demonstrable within such an interval Nevertheless the available material permits only limited conclusions

The deterrents to broad, categoric views arise from deficiencies in basic knowledge It has been theorized that the persistence of abnormal pulmonary vascular resistance after relief of mitral obstruction results because of organic vascular changes However a final statement actually rests with repeated angiographic and pathologic correlations which are not yet available

It also has been inferred that "functional" factors which influence the pulmonary circulation may account for the fall or rise in resistance when the mitral obstruction has been abolished However the exact identity of these "functional" mechanisms and the physiologic events which awaken or retard their effect on the pulmonary circulation actually are quite obscure Questions in this parameter are related to the role of active pulmonary arterial vasoconstriction and of passive vascular distention They also concern the problem of pressure-volume-flow relations in the contrasting structures of a normal and abnormal lung.

Only a clarification of these moot points will expand the usefulness of this demonstration of the various physiologic responses to the relief of mitral valve obstruction

## Discussion

DONALD I would like to show briefly our findings two years after what was considered by the surgeon to be a successful mitral valvotomy There was a very considerable reduction of resting pulmonary arterial pressure after operation Although there was a striking reduction, the levels of pressure achieved *were still above normal in most cases There was a similar fall in wedge* pressure in the majority of cases although many patients with excellent or very good results still had abnormal wedge pressures even at rest The marked decrease in pulmonary vascular resistance in the patients with initial high resistances was very striking Figure 1 relates the degree of fall in pressure

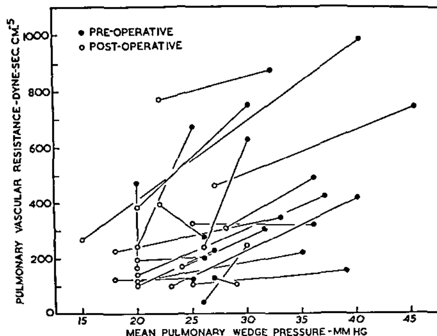



FIG 1 —Individual changes in pulmonary vascular resistance and mean pulmonary wedge pressure after mitral valvotomy

behind the mitral valve and the reduction in pulmonary vascular resistance It will be seen that these go hand in hand in those cases with initially increased pulmonary vascular resistance It would appear therefore that although an increase in wedge pressure does not necessarily cause an increase in pulmonary vascular resistance, a reduction of wedge pressure after valvotomy is almost always associated with a considerable fall in pulmonary vascular resistance.

Our findings during exercise after operation are not quite so satisfactory Some of you may remember that in our 6 month follow-up after mitral valvotomy we were disturbed to find that although the pulmonary arterial pressure was considerably reduced at rest, there was still a marked rise in pulmonary arterial pressure and pulmonary vascular resistance during exertion

We feared that such patients may be able, without the handicap of dyspnea, to place an even greater overload on the right ventricle during repeated exertion every day We found that, although the pulmonary arterial pressure is on the whole reduced during exercise, even the patients with excellent and very good results still showed highly abnormal pulmonary arterial pressures during exertion Each patient exercised at the same level before and after operation

The pulmonary vascular resistance during exercise after operation was also highly abnormal in many cases particularly those with excellent and very good results A number of these cases also showed a slight increase of cardiac output response to exercise after operation and as a result of this, work of the right ventricle during exertion was but little altered by operation Nevertheless both clinical and electrocardiographic studies of these patients two years after mitral valvotomy showed no evidence of increased right ventricular hypertrophy or enlargement The reason why these patients do not experience right ventricular embarrassment despite the marked overload during exercise may be the fact that we found, to our surprise, that the resting cardiac output was significantly reduced in the majority of patients, including all those who had the most satisfactory results The combination of a moderately reduced pulmonary arterial pressure and reduced resting cardiac output results in the resting right ventricular work now being within normal limits in most of these patients (fig 2) It would thus appear that, providing the right ven-

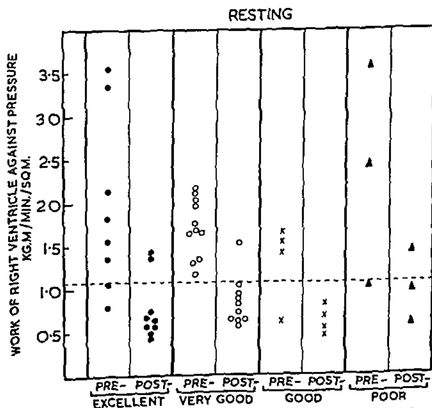



FIG. 2—The work of the right ventricle against pressure at rest before and after mitral valvotomy

tricle is not under stress during long periods of rest which occur in normal everyday life, then it can cope with a very considerable increase in work during periods of exercise

(I wish to thank my colleagues Drs J M Bishop, O L Wade and P N Wormald who collaborated in this follow-up )

DEXTER: I am sorry that I do not have a slide Our experience is limited in this regard, but it has been rather uniform When the valve has been satisfactorily opened, pulmonary vascular resistance has indeed fallen, as Dr Donald has shown High resistances fall very rapidly In two weeks, they fall, not to normal, but very dramatically After six months to a year, they have usually been essentially normal However, in those whose valves have not been opened satisfactorily and in those who have had mitral insufficiency develop as a result of the operation, the pulmonary vascular resistance may remain elevated or even go higher

So it seems to me that our experience has been very much like Dr Donald's

BAY I would like to speculate for a moment on the very interesting question raised by Dr Donald, namely, "why does pulmonary edema develop more readily in patients with mitral stenosis and low pulmonary resistances and relatively normal pulmonary arterial pressures on exercise?"

The work of the left auricle in the presence of mitral stenosis is made up of three components

One, of course, is the work of the auricular musculature itself, which, in this case, does not need to be considered because most of his patients that developed pulmonary edema were fibrillating and, in any case, the situation was the same in the two groups

The second component of the left auricular work is the potential energy stored therein by the preceding left ventricular beat with its regurgitation of blood and pressure This factor is presumably the same in the two groups and we can disregard it

The third factor of left auricle work in mitral stenosis is the potential energy stored there by the right ventricle Presumably the ones with the low pulmonary arterial pressure and the low pulmonary resistance could, by dilatation, produce a great increase in this factor of left auricular work with a tremendous increase in left auricular pressure as opposed to those whose pulmonary arterioles could not dilate A very small increment of activity on the part of the patients in the presence of mitral stenosis requires a great increase in left auricular work to get blood through that narrow orifice, especially with the shortening of diastolic time that comes with increased heart rate Do you hold to that, Dr Donald?

DONALD That might be so, Dr Bay The problem of pulmonary edema in mitral stenosis remains largely unsolved

I do feel that more attempts should be made with modern techniques to define the pressure-volume relationships in the left atrium and pulmonary veins in the various stages of mitral stenosis Differences of pressure-volume relationships such as must occur between the undilated hypertrophied atrium in sinus rhythm and the widely dilated fibrillating atrium, may have a critical effect on the true pulmonary capillary pressure

Dexter. I would like to say a word about the effect of low and high pulmonary vascular resistance on the production of acute pulmonary edema

I have a very definite impression that those who have a low vascular resistance develop edema promptly timewise, with elevation of pulmonary capillary pressure.

Our experience has been that in those who have a very high pulmonary vascular resistance, a high pulmonary "capillary" wedge pressure of 30 to 35 mm Hg may be present for 2 or 3 hours as a result of tachycardia before clinical pulmonary edema appears When therapy is instituted, it may take 2 or 3 hours for pulmonary edema to disappear after the pulse rate returns to normal

I cannot help but feel that the time necessary to produce pulmonary edema at a given elevation of hydrostatic pressure in the pulmonary capillaries is short in the absence of pulmonary vascular disease and prolonged in its presence

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